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Review Article

Management of AML Beyond "3 + 7" in 2019

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ABSTRACT

The therapeutic paradigm for treatment of acute myeloid leukemia (AML) is rapidly changing with the advent of a new generation of drugs targeting diverse aspects of leukemogenesis. Whereas standard treatment for AML until recently consisted of a classic chemotherapy backbone, the incorporation of novel agents targeting pathogenic mutations, myeloid surface markers, and apoptosis-related proteins may become a reality in the next few years. In this review, we outline the therapeutic landscape of recently approved novel agents for AML, including *FLT3* inhibitors, isocitrate dehydrogenase 1/2 (*IDH1/2*) inhibitors, Bcl-2 antagonists, hedgehog signaling inhibitors, and immunotherapy-based approaches. Some of the future challenges in the field would be to delineate which specific patient subsets derive the most clinical benefit from a given novel agent and, furthermore, which drug combinations will yield the maximal antileukemia effect without increased toxicity. To this end, it is expected that advances in genomic and epigenomic classification of AML will facilitate a rational and optimal choice of these novel agents for AML patients.

1. INTRODUCTION

The field of acute myeloid leukemia (AML) is in the midst of experiencing exciting changes in understanding of the pathogenetic basis of leukemogenesis [1], the molecular milieu associated with newly diagnosed AML [2,3], and refractory disease [4]. The recent introduction of several new agents into the prescribed treatment of AML patients further underpins the importance of rational incorporation of these novel therapies into routine practice. Midostaurin, gilteritinib, venetoclax, glasdegib, enasidenib, and ivosidenib are now readily available Food and Drug Administration (FDA)-approved agents which, in the coming years, will form a pivotal part of the evolving armamentarium for treating AML patients. Clinicians are now endowed with the formidable task of streamlining a rational approach for the use of these drugs in AML. Here, we will review and discuss these novel agents, as well as promising new approaches for the treatment of AML. The literature research for this review was undertaken by searching PubMed with the terms "acute myeloid leukemia" or "AML." The search was limited to those papers written in English between January 1, 2016, and February 1, 2019. In addition, abstracts of the 2017 and 2018 American Society of Hematology (ASH) meetings were reviewed for pertinent reports.

2. *FMS*-LIKE TYROSINE KINASE 3 INHIBITORS IN AML—HERE TO STAY?

The receptor tyrosine kinase *fms*-like tyrosine kinase 3 (*FLT3*) presents a bone fide target for rationally designed drugs for AML, owing to its clear role in the pathogenesis of this leukemia, its marked association with aggressive disease, and its high prevalence as seen in up to 30% of AML patients. Indeed, targeting *FLT3* has been the classic example for a clinically actionable mutation, making it an attractive target for investigators and pharmaceutical companies alike, and resulting in the development of a multitude of oral FLT3-targeting agents [5]. However, an advance in this field was brought about when the clinical data with midostaurin combination therapy were published. The practice-changing RATIFY trial introduced into the center stage of AML treatment the immense potential in the incorporation of *FLT3* inhibitors into routine induction chemotherapy in AML [6]. For the first time in nearly four decades, a significant improvement in patient outcome was realized with the addition of midostaurin to the standard backbone of induction therapy "3 + 7" (daunorubucine and cytarabine). Furthermore, additional insights regarding the intricacies of *FLT3* therapy have been accumulating since the initial publication of the trial results. For example, an intriguing investigation on the specific insertion point of the internal tandem duplication of *FLT3* suggested that patients whose ITD insertion site is exclusively in the beta1-sheet region had significantly inferior overall survival compared to patients with other ITD insertion sites [7]. Further complicating the therapeutic picture of midostaurin was an additional interesting observation from the RATIFY trial, suggesting that the therapeutic benefit of midostaurin was most evident in patients without an *NPM1* mutation and with a high allelic *FLT3-ITD* ratio ($NPM1^{wt}$/$FLT3\text{-}ITD^{high}$) [8]. When clinical outcomes were censored at the time of allogeneic stem cell transplantation (ASCT), those patients receiving midostaurin experienced a significant survival benefit compared to placebo-treated patients (26 months *vs.* 14 months) [8]. These emerging data serve

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as a reminder to the complicated picture unfolding with the progressively sophisticated therapies in AML, and the crucial need to analyze study outcomes not only from a clinical perspective, but also from a correlative standpoint to further improve our capacity to choose patient subsets more likely to respond to a given novel agent. Quizartinib (AC-220) is another *FLT3*-targeting agent whose phase 2 data were eagerly awaited. It seems that the wait was worthwhile, as indicated by the results of the international multicenter phase 2 trial of single-agent quizartinib for relapsed/refractory AML patients. Quizartinib monotherapy showed response rates of over 40% in *FLT3-ITD*$^{+}$ patients. Moreover, a response rate of over 30% was seen also in *FLT-ITD*$^{-}$ patients, attesting to the off-target and significant clinical activity of quizartinib [9]. The ongoing Quantum-R study is randomizing relapsed/refractory *FLT3-ITD*$^{+}$ patients to single-agent quizartinib *versus* standard salvage chemotherapy. As presented in the 2018 ASH meeting, the data are clearly indicative of increased response and survival rates in the quizartinib study arm [10]. Gilteritinib is the most recent addition to the FLT3 therapeutic arsenal. Its recent FDA approval was based on the notable results of the phase 1/2 trial in relapsed/refractory patients showing a 40% response rate in this challenging patient population [11]. Importantly, a near complete inhibition of *FLT3* phosphorylation was evident in most patients, further attesting to the potency of this agent. Crenolanib had been previously shown to effect only transient clinical responses when used as a single agent [12], indicating that similarly to midostaurin and, perhaps, also to gilteritinib and quizartinib, its possibly true clinical calling may be in combination regimens. Of note, a recent whole exome interrogation of patients losing response to crenolanib revealed that some patients acquired *NRAS* and *IDH2* mutations, whereas other patients developed new *TET2* and *IDH1* mutations in conjunction with *FLT3* mutations [13], possibly suggesting a role for testing this agent with IDH1/2 inhibitors. A clinical arena being actively mapped is the role of maintenance therapy with FLT3 inhibitors. Sorafenib, for example, was found in an early phase I from the USA to be highly effective in the posttransplant setting [14]. More recent corroboration for the efficacy of sorafenib maintenance was presented by the German/Austrian AML group, who performed a randomized trial for posttransplant patients, showing a 2-year relapse-free survival rate of 53% in the placebo group, *versus* an 85% rate in the sorafenib arm [15]. The RADIUS phase 2 trial looked at midostaurin for *FLT3-ITD* patients who, following ASCT, were randomized to standard of care with or without midostaurin. At 18 months, the risk of relapse was reduced by 46% in the midostaurin group [16]. Contrastingly, a RATIFY trial post hoc landmark analysis focusing on the nontransplanted patient subset who went on midostaurin maintenance following the induction/consolidation sequence did not find a difference in disease-free survival or overall survival between the placebo and the midostaurin arms of the study [17]. Quizartinib may also hold a future role in maintenance therapy following ASCT, as recently shown in a small cohort of *FLT3-ITD*-mutated patients [18]. The therapeutic role of midostaurin is further solidified with a recent publication showing the feasibility of an approach incorporating it into the therapeutic sequence beginning with induction and also following ASCT as maintenance therapy for 12 months [19]. Older patients attained event-free survival and overall survival rates of 53% and 46%, respectively. Clearly, combining standard induction chemotherapy and targeted *FLT3* therapy is of high interest and is being actively explored in the phase 3 QuANTUM-first trial, with preliminary data suggesting acceptable toxicity and high response rates [20]. The use of quizartinib in combination with azacitidine or low-dose cytarabine also seems to be a promising approach, with phase1/2 indicative of response rates of over 70% [21]. The preliminary data from the ongoing phase 1 study combining gilteritinib with induction and consolidation chemotherapy suggest high response rates [22]. The addition of gilteritinib also seems to be safe, from a toxicity standpoint, and has yielded initial response rates [22]. Lastly, combining crenolanib with standard induction chemotherapy also seems to hold promise, as suggested by preliminary results of an ongoing trial (NCT02283177) [23].

The future seems to be promising for *FLT3* inhibitors, as novel agents continue to be developed. One example is FF-10101, a novel irreversible *FLT3* inhibitor designed to overcome the problem of resistance mutations seen in patients progressing on therapy with previous *FLT3* inhibitors [24]. Preclinical data in leukemic cell lines and mouse models suggest that this agent may have potent activity against *FLT3-ITD* and *FLT3-D835*. Aiming to combine immunotherapy with targeting of *FLT3*, investigators undertook a proof of concept preclinical study employing *FLT3*-directed CAR-T cells. Interestingly, the administration of crenolanib in this study facilitated the increased expression of *FLT3* specifically on *FLT3-ITD*$^{+}$ AML cells, and resulted in augmented clearance of these cells by the chimeric antigen receptor T-cells [25] (CAR-T).

3. IDH 1/2- TIME TO DIFFERENTIATE

Improved knowledge of the metabolic foundation of AML over the past decade has resulted in the understanding of the differentiation block experienced by patients with mutations in isocitrate dehydrogenase (*IDH)1* and *IDH2*. These culminate in the production of the oncometabolite 2-hydroxyglutarate (2-HG), leading to aberrant histone hypermethylation and impaired hematopoietic differentiation (reviewed by Medeiros *et al.* [26]). These mutations are not frequent genetic events in the AML patient population (*IDH1* reported in 6–10%, and *IDH2* in 9–13% of patients). Ivosidenib, and enasidenib, oral *IDH1* and *IDH2* inhibitors, respectively, were studied in AML patients, based on their capacity to reduce intracellular levels of 2-HG and induce differentiation in preclinical models of AML.

Enasidenib was studied in a large cohort of *IDH2*-mutated patients with relapsed/refractory AML [27]. The overall response rate was nearly 40%, with 10% of patients being bridged to an ASCT. Importantly, over 40% of transfusion-dependent patients achieved transfusion independence. Differentiation syndrome was experienced by 6% of the study's patients. Several important insights were gained from this analysis. First, the two *IDH2* mutations R140 or and R172 were not different in terms of response or patient survival following treatment with enasidenib. Second, patient outcome was not affected by the underlying cause of the progressive disease, that is, primary refractory AML or relapsed AML. Lastly, there was a clear correlation between reduction of 2-HG levels and complete remission (CR) rates in *IDH2*-R172 patients. It is noteworty that differentiation syndrome, which is considered as the main toxicity with enasidenib was recently assessed to be more likely to occur in patients with fewer prior treatments, and in those with more than 20% bone marrow blasts [28].

The 2018 FDA approval of ivosidenib [29] was based on the results of the AG120-C-001 phase 1 study [30]. It enrolled 179 adults with relapsed/refractory AML with mutated *IDH,* who were administered 500 mg ivosidenib on a daily basis. The notable composite remission rate of over 30%, as well as the 8.2-month median duration of response concomitant to a decreased need for blood product support in 37% of patients were pivotal determinants in drug approval. Strikingly, 21% of the responding patients were found to be MRD negative, further attesting to the potential for deep molecular remissions with this agent. Furthermore, it seemed that patients with *IDH1* responses experienced longer survival. Whether response or resistance to ivosidenib could be predicted via coexistence of mutations in other myeloid disease-related genes was not established, though the investigators noted that the nonresponders were more likely to harbor receptor tyrosine kinase (i.e., *NRAS*, *FLT3*, *PTPN11*, *KRAS*) abnormalities. The typical class effect of differentiation syndrome was seen in 10% of the study cohort. In the recent 2018 ASH meeting, results from the phase 1 trial exploring the use of ivosidenib in untreated AML patients were presented [31]. In this challenging patient population, consisting of a significant secondary AML patient subset with prior hypomethylating drug exposure, differentiation syndrome was seen in 17% of patients, with an overall response rate of nearly 60%, while transfusion independence was attained in 38% of patients.

Despite the justified enthusiasm for this exciting new class of drugs, emerging data regarding resistance mechanisms [32,33] and methylation patterns [34] provide impetus for rational combination therapy. An intriguing question is whether these agents can be safely combined with induction chemotherapy to augment responses. Data emerging from the ASH 2018 meeting on 134 *IDH1*/*IDH2*-mutated patients suggest that this approach is feasible and clinically meaningful for both enasidenib and ivosidenib [35].

4. CPX-351—BACK TO CHEMOTHERAPY

When the first-in-man study of CPX-351 was published in 2011, it became quite clear that the unique liposomal formulation of daunorubicin and cytarabine at a fixed molar ratio of 5:1 is highly effective in AML [36]. The subsequent phase 2 study randomizing older AML patients to either CPX-351 or standard induction showed that CPX-351 was associated with a higher response rate (66% *vs.* 51%), with distinctive superiority in the subset of patients with secondary AML, translating into improved survival in this challenging patient segment [37]. Interestingly, while count recovery was slower in the CPX-351 group, there was no increase in the rate of infection-related or 60-day mortality. The definitive FDA approval [38] of CPX-351 was based on the phase 3 trial randomizing 309 patients with secondary AML aged between 60 and 75 years to CPX-351 or standard induction [39]. The results of this pivotal trial unequivocally showed improved outcomes with regards to overall response (47% *vs.* 33%) and survival (9.5 months *vs.* 5.9 months) in the CPX-351 arm. Investigators from the Fred Hutchinson Cancer Center recently published their experience with attenuated doses of CPX-351, aiming to determine whether these would permit treatment of less fit AML patients [40]. Commendably, their study comprised 48 patients with a median Eastern Cooperative Oncology Group (ECOG) performance status of 2, including patients with an ECOG performance status of 4, and additionally allowed for outpatient care. Their data showed an early mortality rate of 31% with a 12-month survival rate of less than 20%, suggesting that this approach is still suboptimal for the challenging group of unfit AML patients. There may also be a role for CPX-351 in the salvage arena, as indicated by the results of a multicenter phase 2 trial, which randomized 125 patients with relapsed/refractory AML to CPX-351 *versus* investigators' choice for salvage chemotherapy [41]. While the CPX-351 arm was not superior to the control arm, when the whole cohort was analyzed, high-risk patients in the CPX-351 arm benefitted from increased rates of response and overall survival coupled with lower 60- day mortality (16% *vs.* 24%).

Will CPX-351 be incorporated into additional AML clinical settings? An interesting phase 1 study assessed whether CPX-351 can be sequentially combined with fludarabine/busulfan conditioning for refractory AML patients undergoing ASCT [42]. The investigators suggested that given the 1-year leukemia-free survival rate of 27% of this very high-risk patient population, some may derive a benefit from this approach. Finally, we note a recent ASH abstract examining the molecular milieu of CPX-351-treated patients [43]. Analyzing a cohort of 85 patients, the investigators determined that patients with *NPM1* and *IDH1*/*IDH2* mutations were more likely to respond and, conversely, those with *CBL* and *TP53* were more resistant to treatment. Thus, it may be possible to hypothesize that certain patient subsets with de novo AML and specific molecular features may benefit more from CPX-351, as opposed to standard induction chemotherapy, a supposition which would need to be tested in future studies.

5. VENETOCLAX—APOPTOSIS TAKES CENTER STAGE IN AML

Targeting apoptosis is proving to be one of the most exciting fronts in hematology, with Bcl-2 inhibition being the prime example of clinical success in this clinical setting. Venetoclax, an oral Bcl-2 inhibitor, gained marked enthusiasm from its initial arrival, owing to its favorable toxicity profile and impressive single-agent activity in a cohort of 32 high-risk AML patients [44]. The encouraging results in this group of older patients (median age of 71), at least half of whom were post intensive induction chemotherapy and at least 60% had poor-risk cytogenetics, was the initial positive clinical sign that Bcl-2 inhibition was therapeutically significant. This led to a subsequent phase 1b clinical trial, which included combination with azacitidine and decitabine for treatment of naïve older AML patients [45]. The results from this study showed remarkable response rates of over 60% and a favorable safety profile febrile neutropenia being the most common serious adverse event. Importantly, the beneficial effect of venetoclax was not restricted to a specific hypomethylating agent, as patients treated either with decitabine or azacitidine had comparable outcomes. The ensuing expansion study in 145 patients revealed an overall response rate of nearly 70%, coupled with a median duration of response of 11.3 months and median overall survival of 17.5 months [46]. Notably, the study population consisted of patients with a median age of 74 years, with nearly half of them harboring high-risk cytogenetics, further attesting to the outstanding results seen in this challenging cohort of patients. A future role for venetoclax in patients with relapsed/refractory AML will need to be explored, given the recently published study of 43 patients with various myeloid malignancies, showing response rates of around 20% [47].

Interestingly, a recent analysis of leukemia stem cells obtained from azacitidine/venetoclax-treated patients showed that one of the underlying mechanisms of the therapeutic response was the inhibition of the electron transport chain complex II, leading to suppression of the oxidative stress, and subsequent impairment of leukemia stem cell function [48]. Certainly, one of the future challenges of using venetoclax in a rational fashion will be the optimal selection of patients more likely to respond. To this end, correlative data from analysis of AML patients' cells suggest that overexpression of the HOXA and HOXB genes may be associated with increased sensitivity to venetoclax [49]. As novel Bcl-2 inhibitors such as S55746 [50] and navitoclax [51] are being actively studied we expect the field of apoptosis modulation in leukemia to move forward.

6. GLASDEGIB—HARNESSING THE POWER OF HEDGEHOG INHIBITION

The Hedgehog signaling pathway represents a novel therapeutic avenue being evaluated in solid malignancies, as well as more recently in AML. Inhibitors of Smoothened (SMO), a critical transducer of the Hedgehog pathway, have been successfully used in solid cancers and, owing to convincing preclinical [52] and subsequent phase-1 data [53], have been assessed in AML. In a recent phase 1 trial combining glasdegib, an oral SMO inhibitor, with either low-dose cytarabine or decitabine, over 30% of patients achieved a remission with a manageable side effect profile [54]. Another study in previously untreated patients combined glasdegib with standard induction chemotherapy, followed by glasdegib maintenance, revealed a CR rate of 46% with a favorable safety profile [55]. The 2018 FDA approval was based on the results of the phase-2 trial randomizing newly diagnosed unfit patients between low- dose cytarabine monotherapy and combination low-dose cytarabine and glasdegib [56]. Those results showed superior CR rates (2% *vs.* 17%) and overall survival rates (8.8 months *vs.* 4.9 months) for the combined therapy arm. Given the recent introduction of venotoclax and azacitidine/cytarabine for a similar patient population, namely older unfit patients, the exact role glasdegib will assume in AML therapy remains to be determined.

7. IMMUNOTHERAPY IN AML—AN UNFULFILLED PROMISE?

Immunotherapy-based platforms have proven to be exciting and efficacious treatment modalities in acute lymphoblastic leukemia as well as in non-Hodgkin lymphoma, Hodgkin lymphoma, and myeloma. However, the immunologic frontier has been relatively quiescent in AML. Yet, with the recent reintroduction of gemtuzumab ozogamicin (GO) into routine practice (facilitated by the 2017 approval of the US FDA and the European Medicines Agency), immunotherapy is reemerging as a potential robust treatment approach for AML. The efficacy of GO was primarily based on the results of the ALFA-0701 trial [57] which showed that in newly diagnosed AML patients (between the ages of 50 and 70), the addition of GO resulted in an improved rate of event-free survival in those with favorable and intermediate-risk cytogenetics, the results of which were recently updated [58]. These data are also supported by the 2014 meta-analysis of five randomized controlled studies comprising 3325 patients (also including the ALFA-0701 patients) which showed a survival benefit for GO-treated patients [59]. Vadastuximab talirine (SGN33A) is another CD33-targeting monoclonal antibody whose phase 1 data showed promising activity and toxicity profile, both as monotherapy [60] and when combined with hypomethylating therapy [61]. IMGN779 is a novel CD33-targeting antibody–drug conjugate consisting of the DNA alkylator, DGN462, with preclinical data suggestive of significant antileukemia activity [62]. Owing to its ubiquitous expression on AML blasts, CD123 is a prime immunotherapeutic target. SGN-CD123A is an antibody–drug conjugate with encouraging data in preclinical AML models, as well as possible synergism when combined with *FLT3* inhibition in *FLT3*-mutated xenograft models [63]. The bispecific T-cell engager (BiTE) AMG 330, a CD33/CD3-directed BiTE antibody, was introduced a few years ago [64], with potent activity in preclinical studies. The latter agent's upregulation of PD-L1 as a resistance mechanism [65] led to subsequent development of a novel bifunctional checkpoint inhibitory T cell-engaging (CiTE) antibody combining T-cell recruitment to CD33 positive blasts coupled with on-site immune checkpoint blockade [66]. MGD006 (flotetuzumab) is a dual-affinity retargeting (DART) agent formed by the fusion of antibodies to CD3 and CD123, and which directs T-cells to AML blasts, with notable results in preclinical studies [67,68].

CAR-T cell therapy is being vigorously explored for AML. However, the challenge of finding an optimal and safe therapeutic target which would be unique to malignant blasts and not normal hematopoietic stem cells (HSC) is still ongoing in this nascent field [69]. The transmembrane glycoprotein CLL-1, which is preferentially expressed in leukemia stem cells, was recently used as a CAR-T target with promising xenograft activity [70]. *FLT3*-targeting CAR-T cells have also been explored in this setting, with potent activity against AML blasts, albeit at the price of inhibition of normal hematopoiesis due to concomitant targeting of normal HSCs [25]. An innovative approach using compound CAR-T cells targeting both CD123 and CD33 was shown to be highly effective in a murine model of AML [71]. NKG2D ligands are structural homologs of MHC class I molecules, and are expressed at high levels in hematologic malignancies, but rarely in normal tissues. This makes them potentially optimal therapeutic targets, with recent phase I data showed possible antileukemia activity in using NKG2D CAR-T cells in AML patients [72]. Aiming to circumvent the myeloid toxicity associated with using CD33-directed CAR-T cells, investigators from the University of Pennsylvania genetically deleted CD33 in normal HSCs, and showed in a rhesus macaque model that these engineered HSC were capable of normal hematopoiesis without being affected by CAR-T therapy. This provided a proof of concept for the idea of tissue engineering combined with nonmyelotoxic CAR-T therapy for AML [73].

While targeting the PD-1/PD-L1 pathway proved to be effective in the treatment of solid and lymphoid malignancies [74,75], its role in the treatment of AML is not yet firmly established. Nonetheless, preclinical data hint at the possibility of its use in AML [76,77]. Importantly, a phase-1 multicenter study in patients with relapsed hematologic malignancies following ASCT revealed that immune checkpoint blockade with ipilimumab was effective in several patients with extramedullary AML, although immune-mediated toxicity and GVHD were limiting factors in that study [78]. A recent phase-2 study in 77 patients with refractory/relapsed AML showed that combination therapy of azacitidine and nivolumab yielded an overall response rate of 33%, which was above 50% in those patients who were naïve to treatment with azacitidine [79].

Table 1 | Selected ongoing and future clinical trials in AML.

Agent	Clinicaltrials.Gov Registry ID	Phase	Therapeutic Approach/Target	Clinical Setting
Gilteritinib + venetoclax	NCT03625505	I	*FLT3* inhibition	Relapsed/refractory AML
Lentivirally redirected CD123 autologous T cells	NCT03766126	I	CAR-T	Relapsed/refractory AML
Lentivirally redirected CD33 autologous T cells	NCT03126864	I	CAR-T	Relapsed/refractory AML
CPX-351 + gemtuzumab ozogamicin	NCT03672539	I	CD33 Monoclonal antibody	Relapsed/refractory AML
Nivolumab + ipilimumab	NCT03600155	II	Immune checkpoint inhibition	Relapsed/refractory AML following allogeneic stem cell transplantation
Glasdegib + azacitidine	NCT02367456	II	SMO inhibition	Newly diagnosed AML
Crenolanib, midostaurin	NCT03258931	III	*FLT3* inhibition	Crenolanib *vs.* midostaurin maintenance following intensive treatment for newly diagnosed AML
Ivosidenib + venetoclax	NCT03471260	Ib/II	*IDH1*, Bcl-2	*IDH1*-mutated relapsed/refractory AML
Etionstat + azacitidine	NCT01305499	II	HDAC inhibition	Patients over >60 years not fit for intensive induction
Dendritic Cell Fusion Vaccine	NCT03059485	II	Cancer vaccine	AML patients in remission
APR-246 + azacitidine	NCT03072043	Ib/II	TP53	TP53-mutated AML
Merestinib + LY2874455	NCT03125239	I	MET kinase inhibitor, FGFR inhibitor	Relapsed/refractory AML

Abbreviations: AML: acute myeloid leukemia, CAR-T: chimeric antigen receptor T-cells, HDAC: Histone deacetylase, FGFR: Fibroblast growth factor receptor, *FLT3*: Fms-like tyrosine kinase 3, *IDH1*: Isocitrate dehydrogenase 1, SMO: Smoothened.

8. JUST BEYOND THE THERAPEUTIC HORIZON— CUTTING EDGE BASIC SCIENCE APPROACHES FOR AML

What new therapeutic approaches can we expect in the near future? As stated earlier, agents targeting apoptosis are gaining additional momentum. Recent data indicate that targeting of MCl-1, a member of the Bcl-2 protein family, via a novel small molecule, AZD5991, has significant activity both as monotherapy, and in combination with venetoclax in *in vivo* models of AML [80]. VU661013 is another MCL1 inhibitor which is showing promising results in venetoclax-resistant AML cells and in xenograft models [81]. An exciting approach for modulation of p53 activity is being pursued by Ben-Neriah, a group from the Hebrew University. It makes use of inhibition of casein kinase Iα (CKIα), a pivotal regulator of the Wnt signaling cascade, which essentially brings about increased p53 activity leading to an increased antileukemia effect [82]. Notably, in AML mouse models and patient-derived xenograft models, these inhibitors specifically targeted leukemia stem cells with sparing of normal hematopoietic cells, further emphasizing their potential future clinical role. These data are complemented by the recent finding of a genomic region, downstream to the pivotal Myc transcription factor, which is a super enhancer critical for the regulation of Myc expression, and regulation of both normal and malignant hematopoiesis. Future modulation of this highly influential complex may prove to be a component of AML therapy.

Along the same line, targeting of oncogenic transcription factors in leukemia is a much-sought goal. However, owing to the possibility of "collateral damage," due to the effect on multiple effectors of individual transcription factors, it remains a difficult challenge. It may be possible to selectively target- specific subunits of the transcription factor coactivators, as shown by a recent study where the transcription factor MYB was inhibited by selective inhibition of one of its coactivators with a potent antileukemia effect [83]. Epigenetic modulation is a core feature of AML, thus rendering it as a prime therapeutic target. Preclinical data have shown that targeting the lysine-specific demethylase KDM1A by an oral agent, ORY-1001, resulted in differentiation of leukemic blasts and decreased tumor burden in an AML xenograft model [84]. Aiming to disrupt AML-associated downstream signaling of the mitogen-activated protein kinase (MAPK) 1 and MAPK3 (ERK2 and ERK1) via the growth factor receptor-bound protein 2 (Grb2), investigators from the MD Anderson Cancer Center used a Grb2-blocking antisense oligodeoxynucleotide. Data from the phase 1 trial hinted at robust single-agent activity in patients with relapsed/refractory AML [85], possibly augmented with combination low-dose cytarabine. In the same vein, approaches targeting upstream kinases of oncogenic transcription factors involved in AML is another promising therapeutic venue for AML. This was highlighted by a recent study showing that targeting of upstream kinases such as LKB1 or SIK3 decreased production of the MEF2C transcription factor, essential for the propagation of AML [86]. A novel agent against mutated *TP53*, APR-246, was shown to have combined clinical activity with azacitidine in AML patients with mutated *TP53*. A further insight into the metabolic innerworkings of AML was shown in a zebrafish model of AML. In that publication, it was revealed that the differentiation block characteristic of AML involves the expression of genes related to the electron transport chain leading to the activation of adenosine monophosphate-activated protein kinase (AMPK) signaling [87]. Intriguingly, inhibition of AMPK signaling blocked proliferation of AML cell lines with a minimal effect on myeloid cells, potentially pointing to a novel therapeutic target in AML. Lastly, interesting preclinical data suggest that preservation of the integrity of bone marrow vascular niches via deferoxamine provides considerable antileukemia efficacy of chemotherapy

by increasing its delivery, and augments normal hematopoiesis, in improved survival of study animals. This novel approach may prove to be synergistic with current therapies for AML [88].

These studies shine a light on the vast spectrum of possible therapeutic targets in AML. Hopefully some of these investigational therapies will move forward to clinical testing in the coming years.

9. CONCLUSION

Undoubtedly, times are changing for the AML field. The exponential growth of new agents available for treatment will challenge leukemia physicians and endeavor the field to move towards a precision medicine approach, whereby therapy will be custom-made for a given patient based on age, comorbidities, and molecular attributes of his/her disease. As stated earlier, more robust evidence would be needed to make informed decisions regarding the optimal drug combinations. In the absence of head-to-head comparisons of these new agents, physicians will need to carefully navigate the treatment path by balancing potential benefit with expected drug-associated toxicity. Ongoing studies (some of which are outlined in Table 1) will further inform the field and, hopefully, map the future course for patient care in AML.

CONFLICT OF INTEREST

None.

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