Best Practice & Research Clinical Haematology 32 (2019) 101106

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Which novel agents hold the greatest promise in AML?

Courtney D. DiNardo

Department of Leukemia, University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd # 428, Houston, TX, 77030, USA

ARTICLE INFO

Keywords:
Acute myeloid leukemia
AML
Complete response
CR
fms-related tyrosine kinase 3
FLT3
Isocitrate dehydrogenase-1/2
IDH1/2
Overall survival
OS

ABSTRACT

The therapeutic landscape for acute myeloid leukemia (AML) has changed dramatically with the approval of targeted agents, including venetoclax, midostaurin, gilteritinib, ivosidenib, and enasidenib, among others. However, older patients with AML continue to experience poorer outcomes and are in ongoing need of more effective and less toxic regimens. This review examines the efficacy of novel therapeutics and promising combination approaches to further improve outcomes in the treatment of patients with AML.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy that affects approximately 4.3 adults per 100,000 per year in the United States. AML accounts for over 10,000 deaths annually and the median age at diagnosis is around 68 years [1]. The 5-year survival rate for younger patients (18–60 years) is approximately 40%, while it is a dismal 10% for patients above the age of 60 years [2]. Until recently, the treatment of AML relied on a combination of cytarabine and anthracycline, in a standard intensive regimen (7 + 3 chemotherapy), to which most older patients respond poorly. Within the past two years, the therapeutic armamentarium for AML has expanded, with the approval of several agents including CPX-351 (dual-drug liposomal encapsulation of cytarabine and daunorubicin), gemtuzumab ozogamicin ± induction for $CD33^{+}$ AML (humanized anti-CD33 monoclonal antibody conjugated with calicheamicin), venetoclax (selective inhibitor of B-cell lymphoma-2 or BCL-2) in combination with either a hypomethylating agent (HMA) or low-dose cytarabine (LDAC), glasdegib (inhibitor of the hedgehog signaling pathway) plus LDAC, midostaurin (fms-related tyrosine kinase 3 or FLT3 inhibitor) plus induction/consolidation chemotherapy, gilteritinib (FLT3 inhibitor), ivosidenib (isocitrate dehydrogenase-1 or IDH1 inhibitor), and enasidenib (IDH2 inhibitor). As a result, treatment for AML has been revolutionized and recurrent mutations such as *NPM1*, *FLT3*, *CEBPA* and *IDH1/IDH2* are increasingly used to guide therapy decisions [3]. Indeed these advances are expected to improve outcomes for patients; however, several unmet needs prevail. To this end, these approved therapies are currently being investigated in combination with other approved as well as emerging agents for different treatment settings and distinct patient subsets in AML. This paper reviews accumulating experience from a selection of these studies that potentially could address some of the outstanding medical needs of our diverse patients with AML.

Combinations of venetoclax

Venetoclax is an oral selective inhibitor of the anti-apoptotic protein BCL-2 which has demonstrated impressive synergistic anti-

E-mail address: CDiNardo@mdanderson.org.

https://doi.org/10.1016/j.beha.2019.101106

1521-6926/ © 2019 Elsevier Ltd. All rights reserved.

Table 1
Molecular determinants of outcome in venetoclax combinations. CG-cytogenetic risk [6,8].

CR/CRi	HMA + VEN	LDAC + VEN
Intermediate CG	74%	63%
Adverse CG	60%	42%
NPM1 mutant	91%	89%
IDH mutant	71%	72%
FLT3 mutant	72%	44%
TP53 mutant	47%	30%

CG, cytogenetic risk; CR, complete response; CRi, complete response with incomplete blood count recovery; HMA, hypomethylating agent; LDAC, low-dose ara-C; Ven, venetoclax.

leukemic activity in preclinical studies when combined with an HMA. In clinical trials, combining venetoclax with an HMA such as azacitidine among older patients with AML has also been associated with synergistic effects; including a median overall survival of 16.9 months, which is impressive compared to historical expectations with an HMA alone (~10.4 months) [4–6]. Similarly, in older (≥60 years) patients with AML, venetoclax plus LDAC demonstrated rapid and durable remissions that were associated with a median OS of 13.5 months, which also compares favorably to historical expectations of LDAC alone (~5 months) [7,8]. These results have led to the recent accelerated approval of venetoclax in combination with either an HMA or LDAC for newly diagnosed AML or AML ineligible for intensive chemotherapy in adults aged 75 years and older [9]. However, these approved venetoclax combinations are not typically considered curative, and subgroup analyses have suggested molecular determinants of more durable remissions (mutations in *IDH1, IDH2*, *NPM1*) versus less durable (*TP53* mutations or complex cytogenetics) responses (Table 1) [6,8].

In addition to combinations with lower-intensity therapy, the safety and efficacy of venetoclax in combination with intensive chemotherapy is now under investigation. For example, venetoclax in combination with dose-reduced intensive chemotherapy (5 + 2 regimen of cytarabine + idarubicin) is being studied for the treatment of fit, older patients with newly diagnosed AML who are eligible for intensive chemotherapy [10]. As observed, interim results showed an overall complete remission (CR)/CRi (CR with incomplete blood count recovery) rate of 71%, which was even higher (95%) in patients with newly diagnosed AML, and lower (42%) in those with secondary AML [10]. Survival data from this study is not yet available. Additionally, a combination of venetoclax and the FLAG-IDA (fludarabine, cytarabine, idarubicin, granulocyte colony–stimulating factor) regimen is under investigation for the treatment of fit patients with either newly diagnosed or relapsed/refractory (R/R) AML who are eligible for intensive therapy. Interim analysis from the first cohort of relapsed/refractory AML patients demonstrated that 75% of patients achieved CR/CRi, and 50% of responding patients were able to proceed to SCT. Accrual to the phase 2 portion of the trial is now ongoing [11].

Novel small molecule therapeutics

Idasanutlin is an oral murine double minute 2 (MDM2) antagonist that blocks MDM2 interaction with p53 and results in activation of p53 (in the setting of wild-type TP53) resulting in cell cycle arrest and apoptosis, preventing tumor growth. Idasanutlin is being investigated for the treatment of R/R AML in combination with venetoclax [12] or with araC [13] in ongoing trials, with encouraging preliminary results from early phase studies.

TP53 mutations are commonly detected among elderly patients with AML and especially in patients with secondary or therapy-related AML [14], and are associated with particularly poor outcomes. There are no currently approved strategies to target mutant TP53, however there is currently significant interest in APR-246, which is a small molecule that selectively binds to mutant p53 protein, leading to reactivation. Outcomes from a phase 1b trial studying the efficacy of APR-246 in combination with azacitidine indicated 82% CR among patients with TP53 mutant MDS or oligoblastic AML, and this combination is now being investigated in a randomized phase 2 study [15].

IDH1/2 inhibitor combinations

Ivosidenib and enasidenib have been approved as single agents for the treatment of mutant IDH1 and mutant IDH2 R/R AML, respectively. These agents as monotherapy have been associated with a CR rate of approximately 20%, an overall response rate (ORR) of approximately 40%, and a median OS of 9 months [16,17]. These IDH1/2 inhibitors are now being investigated in combination with induction therapy (7 + 3) among adult patients with newly diagnosed mutant IDH1 or mutant IDH2 AML. As shown in Table 2, the CR/CRi rates with 7 + 3 + either ivosidenib or enasidenib are > 70%, ORR > 85%, and 1-year OS is ≥ 75% for both groups, thereby providing the basis for a randomized phase 3 trial [18]. In the older and intensive chemotherapy ineligible population, several combinations with venetoclax or the IDH1/2 inhibitors have been evaluated in the frontline setting. Table 3 shows that many of these combinations are associated with improved outcomes. Additionally, a phase 1b/2 combination study is ongoing to evaluate the effect of ivosidenib and venetoclax with or without azacitidine among patients with IDH1 mutant AML [NCT03471260]. Overall, the treatment paradigm for elderly patients with IDH1/2 mutations is evolving at a rapid pace [19].

Table 2
Frontline treatment of patients with IDH1/2 mutations (induction chemotherapy in combination with ivosidenib/enasidenib) [18].

	Ivosidenib 63 yrs (24–76 yrs), 30% sAML	Enasidenib 63 yrs (27–77 yrs), 37% sAML
CR	71%	56%
CR/CRi/CRp	80%	72%
ORR	88%	85%
12-month OS, %	79	75
Median OS, mos	Not estimable	Not estimable

CR, complete response; CRi, complete response with incomplete hematologic recovery; CRp, complete response with incomplete plate recovery; ORR, overall response rate; OS, overall survival; sAML, secondary acute myeloid leukemia; yrs, years.

Table 3
Frontline options for older patients with IDH1/2 mutations [20].

	Therapy	N	CR/CRi	CR	Ref
BCL-2	Venetoclax + HMA	35	71%	N/A	DiNardo, Blood 2018 [6]
	Venetoclax + LDAC	18	72%	39%	Wei, JCO 2019 [8]
IDH1	AG-120	34	41%	27%	Roboz, ASH 2018 [22]
	FT-2102	3	33%	0%	Watts, Blood 2018 [23]
	AG-120 + AZA	23	70%	57%	DiNardo, Munich 2019 [24]
	FT-2102 + AZA	4	75%	50%	Cortes, ASH 2018 [25]
IDH2	AG-221	37	38%	19%	Pollyea, ASH 2017 [26]
	AG-221 + AZA	6	50%	33%	DiNardo, ASH 2017 [27]

AZA, azacitidine; HMA, hypomethylating agent; LDAC, low dose cytarabine; N/A, not available.

Immune-based therapies and their combinations

Another area of key interest and scientific development over the past decade has been immune-based therapies for AML. Currently, several antibody-drug conjugates (ADC) and bispecific antibodies are under investigation in early phase trials. These include IMGN632 (CD123 ADC), IMGN779 (CD33 ADC), flotetuzumab (CD123xCD3 dual-affinity re-targeting molecule), XmAb 14045 (CD3xCD123), AMG330 (CD3xCD33), AMV564 (CD3xCD33), cusatuzumab (CD70 plus azacitidine), ASP1235 (ADC against FLT3), MCLA-117(CD3xCLL1), among others [20]. The checkpoint inhibitors (ie, PD1, PDL1, CTLA4 inhibitors) are also under active evaluation in AML and recently results from the combination of the PD1 inhibitor nivolumab with azacitidine have been presented. Compared with historical HMA combinations among patients with R/R AML, nivolumab + azacitidine demonstrated encouraging median OS particularly in first salvage patients (10.5 months versus 5.4 months), consistent with other immunotherapy studies where the less pre-treated a patient is, the less exhausted their T-cell repertoire and the increased efficacy of immunotherapy-based therapy. This was further exemplified through correlative work demonstrating that responding patients to nivolumab + azacitidine had significantly higher tumor infiltrating CD3 and CD8 T cells at baseline in their bone marrow aspirates [21]. Thus, immune-based therapies also represent a promising approach for patients with AML.

Conclusions

The recent progress in the AML treatment landscape has heralded a new era of personalized medicine. Despite these advances, older patients with AML continue to have limited options and are still associated with poorer outcomes. Ongoing trials of combination regimens that include approved agents such as venetoclax, ivosidenib, and enasidenib, along with other emerging and less toxic approaches, are expected to expand choices and improve outcomes for these difficult-to-treat patients.

Disclosures

Research support to institution: Abbvie, Agios, Bayer, Calithera, Celgene, Daiichi-Sankyo, Novartis. Consultant/Advisory Board: Abbvie, Agios, Celgene, Daiichi-Sankyo, Jazz, MedImmune, Notable Labs.

Acknowledgement

C.D.D. is supported by The V Foundation for Cancer Research and the MD Anderson Khalifa Clinical Scholar Award.

References

[1] Cancer Stat Facts: leukemia - acute myeloid leukemia (AML) Available at: https://seer.cancer.gov/statfacts/html/amyl.html Accessed June 27, 2019.
[2] Dohner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med 2015;373:1136–52.
[3] DiNardo CD, Perl AE. Advances in patient care through increasingly individualized therapy. Nat Rev Clin Oncol 2019;16:73–4.

[4] Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with > 30% blasts. Blood 2015;126:291–9.
[5] DiNardo CD, Pratz KW, Letai A, Jonas BA, Wei AH, Thirman M, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol 2018;19:216–28.
[6] DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019;133:7–17.
[7] Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 2012;30:2670–7.
[8] Wei AH, Strickland Jr. SA, Hou JZ, Fiedler W, Lin TL, Walter RB, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. J Clin Oncol 2019;37:1277–84.
[9] Guerra VA, DiNardo C, Konopleva M. Venetoclax-based therapies for acute myeloid leukemia. Best Pract Res Clin Haematol 2019;32:145–53.
[10] Wei AH, Chua CC, Tiong IS, Fong CY, Ting SB, Macraild S, et al. Molecular patterns of response and outcome in the chemotherapy and venetoclax in elderly AML trial (CAVEAT study). Blood 2018;132:333. abstr.
[11] DiNardo CD, Albitar M, Kadia TM, Naqvi K, Vaughan K, Cavazos A, et al. Venetoclax in combination with FLAG-IDA chemotherapy (FLAG-V-I) for fit, relapsed/refractory AML patients: interim results of a phase 1b/2 dose escalation and expansion study. Blood 2018;132:4048. abstr.
[12] Daver NG, Pollyea DA, Garcia JS, Jonas BA, Yee KWL, Fenaux P, et al. Safety, Efficacy, pharmacokinetic (PK) and biomarker analyses of BCL2 inhibitor venetoclax (Ven) plus MDM2 inhibitor idasanutlin (idasa) in patients (pts) with relapsed or refractory (R/R) AML: a phase 1b, non-randomized, open-label study. Blood 2018;132:767. abstr.
[13] Montesinos P, Esteve J, Konopleva M, Martinelli G, Ottmann O, Rodriguez-Veiga R, et al. MIRROS: an ongoing randomized phase 3 trial of idasanutlin + ARA-C in patients with relapsed or refractory acute myeloid leukemia. J Clin Oncol 2019;37:TPS7063. abstr.
[14] Prassek VV, Rothenberg-Thurley M, Sauerland MC, Herold T, Janke H, Ksienzyk B, et al. Genetics of acute myeloid leukemia in the elderly: mutation spectrum and clinical impact in intensively treated patients aged 75 years or older. Haematologica 2018;103:1853–61.
[15] Sallman DA, DeZern AE, Steensma DP, Sweet KL, Cluzeau T, Sekeres MA, et al. Phase 1b/2 combination study of APR-246 and azacitidine (AZA) in patients with TP53 mutant myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Blood 2018;132:3091. abstr.
[16] DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med 2018;378:2386–98.
[17] Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant-IDH2 relapsed or refractory acute myeloid leukemia. Blood 2017;130:722–31.
[18] Stein EM, DiNardo CD, Fathi AT, Mims AS, Pratz KW, Savona MR, et al. Ivosidenib or enasidenib combined with induction and consolidation chemotherapy in patients with newly diagnosed AML with an IDH1 or IDH2 mutation is safe, effective, and leads to MRD-negative complete remissions. Blood 2018;132:560. abstr.
[19] Buege MJ, DiPippo AJ, DiNardo CD. Evolving treatment strategies for elderly leukemia patients with IDH mutations. Cancers 2018;10:187.
[20] Assi R, Kantarjian H, Ravandi F, Daver N. Immune therapies in acute myeloid leukemia: a focus on monoclonal antibodies and immune checkpoint inhibitors. Curr Opin Hematol 2018;25:136–45.
[21] Daver N, Garcia-Manero G, Basu S, Boddu PC, Alfayez M, Cortes JE, et al. Efficacy, safety, and biomarkers of response to azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia: a nonrandomized, open-label, phase II study. Cancer Discov 2019;9:370–83.
[22] Roboz GJ, DiNardo CD, Stein EM, de Botton S, Mims AS, Prince GT, et al. Ivosidenib (AG-120) induced durable remissions and transfusion independence in patients with IDH1-mutant untreated AML: results from a phase 1 dose escalation and expansion study. Blood 2018;132:561. abstr.
[23] Watts JM, Baer MR, Lee S, Yang J, Dinner SN, Prebet T, et al. A phase 1 dose escalation study of the IDH1m inhibitor, FT-2102, in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). J Clin Oncol 2018;36:7009. abstr.
[24] DiNardo CD, Stein AS, Stein EM, Fathi AT, Frankfurt O, Schuh AC, et al. Mutant IDH1 inhibitor ivosidenib (IVO; AG-120) in combination with azacitidine (AZA) for newly diagnosed acute myeloid leukemia (ND AML). J Clin Oncol 2019;37:7011. abstr.
[25] Cortes JE, Watts J, Prebet T, Schiller GJ, Lee S, Yang J, et al. FT-2102, an IDH1m inhibitor, in combination with azacitidine in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS): results from a phase 1 study. Blood 2018;132:1452. abstr.
[26] Pollyea DA, Tallman MS, De Botton S, DiNardo CD, Kantarjian HM, Collins RH, et al. Enasidenib monotherapy is effective and well-tolerated in patients with previously untreated mutant-IDH2 acute myeloid leukemia (AML). Blood 2017;130:638. abstr.
[27] DiNardo CD, Stein AS, Fathi AT, Montesinos P, Odenike O, Kantarjian HM, et al. Mutant isocitrate dehydrogenase (mIDH) inhibitors, enasidenib or ivosidenib, in combination with azacitidine (AZA): preliminary results of a phase 1b/2 study in patients with newly diagnosed acute myeloid leukemia (AML). Blood 2017;130:639. abstr.