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How I Treat

How I treat acute myeloid leukemia in the era of new drugs

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The acute myeloid leukemia (AML) treatment landscape has changed substantially since 2017. New targeted drugs have emerged, including venetoclax to target B-cell lymphoma 2, midostaurin and gilteritinib to target FLT3, and ivosidenib and enasidenib to target mutant isocitrate dehydrogenase 1 and 2, respectively. Other additions include reapproval of gemtuzumab ozogomycin to target CD33, glasdegib to target the hedgehog pathway, and a liposomal formulation of daunorubicin and cytarabine (CPX-351). Genomically heterogeneous AML has a tendency to evolve, particularly under selective treatment pressure. For decades, treatment decisions have largely centered around chemotherapy drug intensity. Physicians now have access to an increasing number of drugs with novel mechanisms of action and distinctive side-effect profiles. Key issues faced by hematologists in this era of new drugs include (1) the timely identification of actionable mutations at diagnosis and at relapse; (2) deciding which drug to use among several therapeutic options; and (3) increasing awareness of how to anticipate, mitigate, and manage common complications associated with these new agents. This article will use 3 case presentations to discuss some of the new treatment challenges encountered in AML management, with the goal of providing practical guidance to aid the practicing physician. (*Blood*. 2020;135(2):85-96)

Introduction

Prior articles in the How I Treat series on acute myeloid leukemia (AML) have focused on acute promyelocytic leukemia, treatment of hematologic emergencies, intensive chemotherapy, management of older individuals, patients with hyperleukocytosis or preexisting comorbidities, and relapsed and refractory FLT3-mutant AML (Table 1). The recent wave of new drug approvals by the US Food and Drug Administration (FDA) (Tables 2 and 3) has created overlapping treatment options, especially in older, unfit populations, as well as in refractory/relapsed patients. Although these new therapies are a welcome advance for patients with AML, this "abundance of riches" also introduces new challenges for the treating physician. Key issues now include (1) the need for timely identification of actionable mutations, not just at diagnosis but also at relapse, (2) deciding which drug to use when several therapeutic options may be available, and (3) the need for increased awareness of how to anticipate, mitigate, and manage common complications associated with these new agents. Most clinical trial publications do not inform clinicians about how to manage emergent toxicities, and review papers predominantly focus on efficacy. In this newest addition to the How I Treat AML series, we present 3 case studies that illustrate how we select and use some of the recently approved AML therapies in the clinic, with practical guidance pertaining to the management of anticipated drug-related complications.

Patient 1: an elderly woman with previously untreated AML

A 75-year-old woman presented with progressive shortness of breath and fatigue over a 6-month period. Blood work demonstrated: a white blood count (WBC) of 26 × 10^9/L with 79% blasts; hemoglobin, 89 g/dL; neutrophils, 0.76 × 10^9/L; and platelets, 28 × 10^9/L. The bone marrow was infiltrated with 94% myeloblasts that were immunophenotypically $CD34^+$, $CD117^+$, $CD13^+$, and $CD33^+$. The karyotype showed trisomy 13, and molecular profiling revealed RUNX1, ASXL1, and SRSF2 mutations. Biochemistry revealed a mildly increased serum lactate dehydrogenase (1.3× upper limit of normal [ULN]) and creatinine (1.4× ULN). She had an Eastern Cooperative Oncology Group (ECOG) performance score of 2.

Question Should this patient receive intensive chemotherapy (ie, 7 + 3 plus or minus gemtuzumab ozogamicin [GO], CPX-351, low-dose cytarabine [LDAC] plus or minus glasdegib or venetoclax, or a hypomethylating agent [HMA] plus or minus venetoclax)?

Proposed treatment

For all patients and whenever possible, enrollment in a clinical trial is our first consideration. Additionally, we recommend rapid screening for actionable mutations (ie, FLT3, isocitrate dehydrogenase 1 and 2 [IDH1 and IDH2]), as FLT3 inhibitors, ivosidenib, or enasidenib, respectively, are either FDA approved or listed in the National Comprehensive Cancer Network (NCCN) compendium for patients ≥75 years, or considered unfit for intensive chemotherapy.

Although some older patients benefit from intensive chemotherapy, several prognostic scoring systems are available that estimate early mortality with intensive chemotherapy in patients ≥65 years with various comorbidities. Given her age of ≥75 years, her baseline renal impairment, and an ECOG ≥ 2, the risk of early mortality was likely to be high.[1] In addition, the European

Table 1. Previous How I Treat articles on AML

Authors	Previous editions	Year
Tallman and Altman[48]	How I treat acute promyelocytic leukemia	2009
Rowe and Tallman[49]	How I treat acute myeloid leukemia	2010
Zuckerman et al[50]	How I treat hematologic emergencies in adults with acute leukemia	2012
Thol et al[51]	How I treat refractory and early relapsed acute myeloid leukemia	2014
Ossenkoppele and Löwenberg[52]	How I treat the older patient with acute myeloid leukemia	2015
Röllig and Ehninger[53]	How I treat hyperleukocytosis in acute myeloid leukemia	2015
Ofran et al[54]	How I treat acute myeloid leukemia presenting with preexisting comorbidities	2016
Pratz and Levis[55]	How I treat FLT3-mutant AML	2017

LeukemiaNet (ELN) 2017 risk classification, which has been applied to patients ≥75 years receiving intensive chemotherapy, suggests that 2-year survival is likely to be <20% for this patient with adverse ELN risk (RUNX1 and ASXL1 mutations).[2,3] Therefore, cytotoxic options such as intensive chemotherapy plus or minus GO and CPX-351 were eliminated. Response rates for LDAC or HMA alone in AML are underwhelming (18% to 28%) and associated with a relatively slow time course to complete remission (median, 3-4 months).[4,5] Glasdegib, an inhibitor of smoothened in the hedgehog signaling pathway, is 1 of 3 recently FDA-approved drugs for use in older or unfit patients with AML (Table 2). Although glasdegib in combination with LDAC had superior survival compared with LDAC alone in a randomized trial, the overall response rate (complete remission [CR]/CR with incomplete hematologic recovery [CRi]) for glasdegib remained modest (27% vs 5%).[6]

A noteworthy recent advance in the treatment of patients with newly diagnosed AML unfit for intensive chemotherapy is the oral B-cell lymphoma 2 (BCL-2) inhibitor venetoclax in combination with either HMA or LDAC.[7,8] Response rates ranged between 54% to 67%, with responses usually achieved after 1 to 2 cycles of therapy and with low early mortality (3% to 6%). Patients with RUNX1 or SRSF2 mutations were reported to have a CR/CRi rate of 81% and 71% to venetoclax-based therapy, respectively.[9] Therefore, in the absence of an actionable mutation, venetoclax plus azacitidine was commenced in this patient, based on the high and rapid response rate and the low rate of early mortality observed with this regimen.

Management and outcome

The patient had an elevated risk of tumor lysis syndrome (TLS) at initiation of venetoclax-based therapy due to a presenting WBC

Table 2. Recent FDA approvals in newly diagnosed AML

Drug/regimen	FDA approval indication[56]	Age in study, y	N	ORR, %	CR, %	CRi, %	30-d early death, %	Survival
Rydapt[57]/midostaurin + IC	$FLT3^{MUT}$ AML	18-59	360	—	59	N/A	4.5	51.4% at 4 y
Vyxeos[58]/CPX-351 liposomal daunorubicin HCl and cytarabine	tAML, AML MRC	60-75	153	47	37	10	5.9	Median, 9.6 mo
Mylotarg[59]/GO	Newly diagnosed adults with $CD33^{+}$ AML with IC	50-70	135	81	70	11 (CRp)	3.8	Median, 27.5 mo
Daurismo[6]/glasdegib + LDAC	>75 yo or unfit for IC	63-92	88	27	17	10	N/A	Median, 8.8 mo
Venclexta[60]/venetoclax + HMA	New AML ≥75 y or unfit*	65-86	145	67	37	30	3	Median, 17.5 mo
Venclexta[8]/venetoclax + LDAC	New AML ≥75 y or unfit*	63-90	82	54	26	28	6	Median, 10.1 mo
Tibsovo[61]/ivosidenib	New AML ≥75 y or unfit* with IDH1MUT	64-87	34	42	30	12 (CRh)	N/A	N/A

—, not available; AML MRC, AML with myelodysplasia-related changes; CR, complete remission; CRh, CR with hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with platelet recovery; GO, gemtuzumab ozogomycin; HMA, hypomethylating agent; IC, intensive chemotherapy; LDAC, low-dose cytarabine; N/A, not available; ORR, overall response rate; t-AML, therapy-related AML; yo, years old.

*Adult patients with newly diagnosed AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

Table 3. Recent FDA approvals for relapsed/refractory AML

Drug/regimen	FDA approval indication[56]	Age in study, y	N	ORR, %	CR, %	CRi, %	30-d early death, %	Survival, median no. of mo
Mylotarg[59]/GO	RR adults or pediatric patients ≥2 y with $CD33^+$ AML with IC	50-70	135	81	70	11 (CRp)	3.8	27.5
Tibsovo[44]/ivosidenib	RR $IDH1^{MUT}$	18-89	258	34	22	12	7	8.8
Idhifa[62]/enasidenib mesylate	RR $IDH2^{MUT}$	19-100	214	29	20	9	5	8.8
Xospata[27]/gilteritinib fumarate	RR $FLT3^{MUT}$	19-85	247	34	21	13 (CRh)	2	9.3

RR, relapsed/refractory. See Table 2 for expansion of other abbreviations.

>25 × 10^9/L, elevated lactate dehydrogenase, and baseline renal impairment.[10] She was hospitalized for titrated cytoreduction with hydroxycarbamide to lower the WBC, commencement of TLS prophylaxis with IV hydration and allopurinol, and biochemical surveillance during the venetoclax dose ramp-up phase (Table 4).

After 48 hours, the WBC fell to <15 × 10^9/L and treatment was initiated with a venetoclax dose ramp-up starting at 100 mg on day 1, 200 mg on day 2, and 400 mg planned for days 3 to 28, combined with azacitidine 75 mg/m^2 per day on days 1 to 7.[7] Severe marrow suppression followed, with a platelet nadir of 8 × 10^9/L on day 11 and a neutrophil nadir of 0.00 × 10^9/L on day 22. The patient was commenced on posaconazole when the neutrophil count dropped to <0.5 × 10^9/L, which necessitated a reduced venetoclax dose due to the pharmacokinetic interaction with CYP3A4 inhibitors (Table 4).[11] The regimen was well tolerated, with the major complication being a urine infection requiring antibiotics. Due to severe treatment-induced pancytopenia, a bone marrow aspirate was performed on day 24, showing a markedly hypocellular marrow without an excess of blasts. As the neutrophil count remained <0.5 × 10^9/L despite marrow blast clearance, venetoclax dosing was interrupted and granulocyte colony-stimulating factor (G-CSF) commenced on alternate days. Six days later, the neutrophil count recovered to 1.8 × 10^9/L. Posaconazole was ceased and the patient was given a brief treatment holiday until platelet recovery to ≥50 × 10^9/L 2 weeks after ceasing venetoclax. Cycle 2 was then commenced with venetoclax 400 mg per day from day 1 (without concurrent azoles) for a planned 28 days (no dose ramp-up necessary). The neutrophil count fell to <0.5 × 10^9/L in the fourth week of cycle 2. Venetoclax was again interrupted and intermittent G-CSF commenced, which led to neutrophil recovery 4 days later. During cycle 2, grade 4 thrombocytopenia lasted 26 days and so for cycle 3, venetoclax duration was truncated to 21 days. A similar pattern in cycle 3 led to a further reduction in venetoclax duration to 14 days for cycle 4. In cycle 4, only a brief period of grade 4 thrombocytopenia was recorded. Therefore, venetoclax 400 mg per day days 1 to 14 was chosen as the optimal dose for this patient. The patient received a total of 12 cycles of therapy and then elected to cease treatment due to fatigue and ongoing treatment burden. Thirty months after diagnosis, cytopenias developed and a bone marrow confirmed relapsed AML. Repeat genomic annotation is recommended at the time of relapse, and this reevaluation identified cytogenetic evolution (complex karyotype with monosomy 17p) and 2 new TP53 mutations (TP53 G154V and TP53 A161T), suggesting biallelic TP53 abnormalities.

Comments

In phase 1b/2 trials, the optimally tolerated dose of venetoclax was 600 mg in combination with LDAC and 400 mg in combination with HMA (azacitidine or decitabine). Higher doses were associated with a greater frequency of delayed count recovery resulting in dose delays. The occurrence of TLS was rare in the original trials, likely a result of the required TLS mitigation strategies, as well as a lower intrinsic risk of TLS with venetoclax in myeloid compared with lymphoid malignancies. Although TLS was uncommon in clinical trials, this was achieved through implementation of TLS risk-mitigation practices (see Table 4). We find that venetoclax-based regimens administered to patients with hyperleukocytosis, particularly in the presence of venetoclax-sensitive nucleophosmin (NPM1) and/or IDH mutations, may lead to life-threatening TLS and should be delayed until effective cytoreduction has been achieved (Table 4).

Venetoclax in combination with HMA or LDAC may induce severe marrow suppression leading to significant and prolonged cytopenias. Management requires a combination of dose interruption, dose delay, dose duration reduction, and other supportive care measures (see Table 4). During the first cycle, we recommend a bone marrow assessment between days 21 and 28. In the setting of blast clearance (<5%), hematopoietic recovery can be assisted by interrupting venetoclax dosing and commencing G-CSF if there is ongoing severe neutropenia. Recovery may occur after only a few doses of G-CSF. If prophylactic drugs with CYP3A4 inhibitory activity are used, such as certain fluoroquinolones (ciprofloxacin) or antifungal azoles, venetoclax dose adjustments are necessary (see Table 4). After remission is achieved, if prolonged grade 4 neutropenia and/or thrombocytopenia is observed, further venetoclax dose interruptions, subsequent cycle dose duration reductions, and/or HMA dose reductions may be necessary to achieve an optimally tolerated dose, as illustrated in our case. Although the effectiveness of various reduction strategies has never been compared, we find that venetoclax dose duration reductions to 14 to 21 days per cycle is often necessary to prevent recurrent prolonged cytopenias (see Table 4).

Although venetoclax combinations may lead to durable responses in some patients, this case highlighted the potential for

Table 4. Summary of our recommendations for venetoclax administration

Issue	Management
Target drug doses	Venetoclax 400 mg/d × 28 d + azacitidine 75 mg/m² days 1-7 or decitabine 20 mg/m² daily days 1-5 subcutaneously or IV OR Venetoclax 600 mg/d × 28 d + LDAC 20 mg/m² daily days 1-10 subcutaneously
Prevention of TLS	Identify patients with higher risk of TLS: WBC >25 × 10^9/L, uric acid above 7.5 mg/dL (446 μmol/L), creatinine above 1.4 mg/dL (124 μmol/L) All patients, especially those with an elevated risk of TLS should be hospitalized until at least completion of ramp-up dosing Prior to commencing venetoclax • For patients with hyperleukocytosis, commence hydroxycarbamide or flat-dose ara-C, eg, 100-1000 mg IV daily until the WBC is <25 × 10^9/L prior to starting venetoclax • Commence TLS prophylaxis with prehydration and uricosuric agents and normalize potassium, inorganic phosphorus, and uric acid levels according to institutional practice • For some molecularly defined AML subsets with high sensitivity to venetoclax, eg, newly diagnosed NPM1 or IDH mutation, we have noticed TLS may even occur in patients with a WBC <25 × 10^9/L; such patients should be monitored carefully for rapid cytoreduction and early onset of severe hyperkalemia; in such cases, we also consider lowering the starting WBC <10 × 10^9/L to lower TLS risk prior to initiation of venetoclax Ramp-up initial venetoclax dosing in steps: 100 mg day 1, 200 mg day 2, 400 mg day 3 (for HMA), 600 mg day 4 (for LDAC) Monitor for TLS complications predose (<4 h) and 6-8 h after each ramp-up dose with additional monitoring until normalization of abnormal biochemistry If significant biochemical or clinical TLS is observed, delay further venetoclax dosing until resolution
Optimize venetoclax dosing	Take venetoclax within 30 min after a meal with ~1 cup of water If HMA used, consider antiemetic prophylaxis (eg, ondansetron) Before commencing venetoclax, patients should have at least a 3-day washout from drugs with CYP3A4 inhibitor activity, as well as grapefruit juice, Seville oranges, and starfruit[11]; CYP3A4 inducers should be avoided; the venetoclax dose ramp-up should reach 400 mg before combination with CYP3A4 inhibitors is commenced; for combination with moderate CYP3A4 inhibitors (eg, ciprofloxacin, fluconazole, or isavuconazole), reduce the venetoclax daily dose by 50% (eg, from 400 mg to 200 mg); if strong CYP3A4 inhibitors are used (eg, voriconazole or posaconazole), we recommend reducing the venetoclax daily dose by at least 75% (eg, from 400 mg to 100 mg); pharmacokinetic studies have shown that venetoclax 50 mg daily when coadministered with posaconazole 300 mg daily most closely resembles the pharmacokinetic characteristics of venetoclax 400 mg daily without posaconazole[11]; therefore, for patients with persistent venetoclax-related adverse events (eg, neutropenia) when coadministered with strong CYP3A4 inhibitors, a further dose reduction of venetoclax to 50 mg should be considered.
Preventing infection	Severe and prolonged neutropenia is common with these regimens, even after achieving remission. For patients with grade 4 neutropenia (<0.5 × 10^9/L), antifungal prophylaxis according to institutional practice; if CYP3A4 inhibitors are used (eg, ciprofloxacin and/or azole antifungals), venetoclax dose adjustment is required (see optimizing venetoclax dosing) Hospitalization until hematologic recovery should be considered for selected patients with a high risk of complications or inadequate social support networks to enable safe outpatient management Treatment-related neutropenia may occur in the later part of the cycle and recover rapidly with commencement of G-CSF
Managing myelosuppression	Postinduction marrow assessment should be performed on days 21-28; if blast excess persists, commence the next cycle without treatment dose interruption If marrow blasts <5%, hold venetoclax and start next cycle when there has been at least partial hematologic recovery (neutrophils ≥0.5 × 10^9/L and platelets ≥50 × 10^9/L); G-CSF may be used to accelerate neutrophil recovery if neutrophils <0.5 × 10^9/L In subsequent cycles (for patients with <5% marrow blasts), monitor blood counts ~ weekly; if treatment-related grade 4 neutropenia persists for >7 days, or the patient develops severe complications, interrupt venetoclax dosing, and start G-CSF until neutrophil recovery We do not reduce the venetoclax dose to manage myelosuppression Consider shortening venetoclax duration for subsequent cycles if hematologic recovery takes >14 days after interrupting venetoclax for neutropenia and/or thrombocytopenia; the following stepwise reductions could be considered 28 days → 21 days → 14 days; consider reducing HMA dose intensity by 50% if marrow cellularity is 15% to 30%, or to 33% dose intensity if marrow cellularity <15% in the setting of clinical response with delayed or lack of hematologic recovery Prophylactic G-CSF after HMA (day 8) or LDAC (day 11) could be considered for patients with recurrent dose delays due to neutropenia
Patients with hepatic impairment	In subjects with severe hepatic impairment (Child-Pugh C), reduce venetoclax dose by 50%
Patients with renal impairment	If GFR >30 mL/min, no venetoclax dose adjustment is necessary If GFR <30 mL/min, no literature exists on venetoclax pharmacokinetics

ara-C, cytarabine; GFR, glomerular filtration rate; TLS, tumor lysis syndrome. See Table 2 for expansion of other abbreviations.

Table 4. (continued)

Issue	Management
When to cease therapy?	Median time to response is 1-2 cycles with venetoclax combinations; if there has not been a meaningful blast reduction or hematologic response after 3-4 cycles of therapy, consider ceasing treatment if effective alternate options exist
Markers associated with outcome	The presence of NPM1 and/or IDH mutation is associated with high rates of clinical response The presence of signaling mutations, particularly FLT3-ITD, and/or biallelic TP53mut may be enriched at relapse (C.D.D. and A.H.W., manuscript submitted, October 2019)

ara-C, cytarabine; GFR, glomerular filtration rate; TLS, tumor lysis syndrome. See Table 2 for expansion of other abbreviations.

clonal evolution in association with clinical progression. Emergence of new or rising levels of kinase mutations (eg, FLT3–internal tandem duplication [ITD]) or mutant TP53 may be observed at the time of relapse (C.D.D. and A.H.W., manuscript submitted, October 2019). Repeat molecular evaluation may therefore have utility in identifying potentially actionable targets at the time of treatment failure.

In contrast, the presence of NPM1 and/or IDH mutations may be associated with a high rate of durable remissions. With azacitidine alone, historical response rates in older patients with NPM1-mutant AML are reported to be 36%, with a median overall survival (OS) not significantly different from patients with wild-type NPM1.[12] For patients with NPM1 mutation, the CR/CRi rate with venetoclax combined with LDAC/HMA is 93%, with relapse-free survival exceeding 4 years in some cases.[9] We have observed NPM1 measurable residual disease clearance that has been sustained for over 2 years in some patients. Therefore, for patients with NPM1-mutant AML, we recommend venetoclax-based therapy as the treatment of choice in unfit older patients.

Patient 2: a young man with relapsed FLT3-ITD–mutant AML

A 36-year-old man presented with gingival swelling, low-grade fevers, and epistaxis. He had a WBC of 44 $\times$ 10^9/L, hemoglobin of 68 g/L, and platelets of 22 $\times$ 10^9/L. Bone marrow examination revealed AML with 72% blasts and monocytic phenotype. His ECOG performance score was 0. Induction was commenced with 7 + 3 (daunorubicin 60 mg/m^2 days 1-3 and cytarabine 200 mg/m^2 per day, days 1-7). Genomic analysis revealed a normal diploid karyotype with NPM1mut, DNMT3A R882mut, and FLT3-ITD (mutant-to-wild-type allelic ratio, 0.6). Midostaurin 50 mg twice daily was commenced on days 8 to 21 of induction. He tolerated induction well and a day 28 marrow demonstrated <5% blasts with count recovery, consistent with CR. The patient received consolidation therapy with high-dose cytarabine 3 g/m^2 twice daily on days 1, 3, and 5, combined with midostaurin 50 mg twice daily on days 8 to 21. A hematopoietic stem cell transplant (HSCT) in first CR was planned and an unrelated donor search initiated as he was an only child, with a goal to proceed to HSCT as soon as possible. During first consolidation, he developed neutropenic fever complicated by typhlitis and pancolitis resulting in significantly delayed administration of additional therapy. Unfortunately, relapsed AML was detected with peripheral blood leukocytosis (35 $\times$ 10^9/L) comprising 48% blasts. Repeat molecular testing confirmed recurrence of the NPM1, FLT3-ITD, and DNMT3A mutations.

Question Should this patient receive intensive salvage chemotherapy or gilteritinib?

Proposed treatment

We propose that this patient commences gilteritinib. The patient was started on gilteritinib 120 mg orally daily. Blood counts were performed twice weekly to monitor for severe differentiation syndrome, which may occasionally occur. Within the first 2 weeks, a reduction in peripheral blasts was noted. Neutrophil and platelet recovery occurred during the second cycle, and a bone marrow examination on day 28 of cycle 2 showed 12% blasts, consistent with a partial response. By the end of cycle 3, CR was attained with <5% bone marrow blasts, and transition to HSCT was reinitiated. By the end of cycle 4, neither the NPM1 nor FLT3-ITD mutations were detectable by polymerase chain reaction (PCR) and capillary electrophoresis. The DNMT3A mutation persisted. The patient proceeded to unrelated donor HSCT in CR2. Gilteritinib was held 7 days prior to the start of his preparative regimen, due to the prolonged half-life and potential risk of contributing to transplant-associated liver injury. Gilteritinib was resumed 45 days post-transplant, after confirmation of successful engraftment with sustained neutrophils >0.5 $\times$ 10^9/L, platelets >50 $\times$ 10^9/L, and absence of graft-versus-host disease (GVHD). Three weeks after recommencing gilteritinib, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) rose to >4$\times$ ULN (grade 2 severity) and gilteritinib was held. A liver biopsy revealed non-specific drug injury, without evidence of GVHD, viral inclusions, or other pathology. The AST/ALT returned to grade 1 within 10 days, and gilteritinib was restarted at a reduced dose of 80 mg daily. The patient remains in CR, now 8 months posttransplant.

Initial therapy for patients with FLT3-ITD AML

At diagnosis, NPM1 and FLT3-ITD represent 2 of the most frequently occurring mutations in AML.[13] Rapid molecular screening is essential as FLT3-ITD is an actionable mutation, and the FLT3 inhibitor midostaurin in combination with intensive chemotherapy has been shown to improve OS in patients 18 to 59 years of age with newly diagnosed FLT3-mutant AML (RATIFY trial).[14] FLT3-ITD allelic ratio and NPM1 mutation status are used to stratify AML risk in both the ELN 2017 classification[2] and the NCCN AML clinical practice guidelines (version 1.2020, 13 August 2019). It must be recognized, however, that FLT3-ITD allelic ratio quantitation is not widely standardized and that the FLT3-ITD allelic ratio threshold of 0.5 should be considered in the context of other clinical and laboratory risk factors.[15,16] Furthermore, our patient had "triple-positive" NPM1mut, DNMT3Amut, and FLT3-ITD AML, which may signify a worse prognosis compared with patients with NPM1mut/FLT3-ITD without DNMT3Amut.[13] In our patient with NPM1mut, given the high FLT3-ITD allelic

ratio and presence of DNMT3Amut, transplant in first CR was planned.

Although not directly related to patient 2, the clinician should note that FLT3 mutations may also be present in patients with favorable-risk karyotype (ie, core-binding factor [CBF] AML, or acute promyelocytic leukemia [APL]). In the case of APL, FLT3-ITD does not appear to have prognostic impact among patients receiving arsenic–all *trans* retinoic acid–based therapy.[17,18] For patients with CBF AML, only 29 such patients with FLT3 mutation were enrolled in the RATIFY trial incorporating midostaurin.[14] Therefore, it is not clear whether there is a beneficial role for FLT3 inhibitors in FLT3-mutant CBF AML. In contrast, the addition of the antibody-drug conjugate GO has been shown in a meta-analysis of conventional intensive chemotherapy regimens to be associated with a 20% improvement in 5-year OS for patients with CBF AML.[19] In contrast, the absolute survival benefit in patients with intermediate-risk karyotype was modest, whereas no clinical benefit was evident for patients with adverse-risk karyoytpe.[20] Although retrospective subgroup analyses suggest that patients with FLT3-ITD,[21] NPM1 mutation,[22] or high CD33 blast expression[23] may benefit from the addition of GO to chemotherapy, the role of GO outside of favorable-risk karyotype remains an important area of debate and ongoing clinical research.

Salvaging FLT3-ITD AML with conventional chemotherapy or FLT3 inhibitors?

A feature of FLT3-ITD is the increased risk of relapse, as was the case in our patient. FLT3 mutations are often subclonal and may be gained or lost at relapse, especially in late or posttransplant relapses.[24,25] Therefore, it is important to repeat FLT3 molecular testing to confirm persistence of the mutation when considering second-line targeted therapies.

Two randomized trials (QuANTUM-R [quizartinib] and ADMIRAL [gilteritinib]) have demonstrated that second-generation FLT3 inhibitors as single agents are associated with superior response rates and improved OS, compared with standard chemotherapy approaches in patients with relapsed or refractory FLT3-mutant AML.[26,27] In the QuANTUM-R study, survival for patients receiving quizartinib was 6.2 months, compared with 4.7 months for standard chemotherapy.[26] Secondary benefits included a higher CR/CRi rate (48% vs 27%) and enhanced likelihood of transition to HSCT among patients randomized and salvaged with quizartinib (38%) vs chemotherapy with mitoxantrone, etoposide, and cytarabine or fludarabine-cytarabine-filgrastim-idarubicin (20%).[26]

Unlike quizartinib, gilteritinib has activity against both FLT3-ITD and/or FLT3-D835 mutations. Dose-optimization studies verified activity at doses ≥80 mg.[28] The pivotal phase 3 ADMIRAL study for first relapse (61%) or primary refractory (39%) FLT3-mutant AML compared gilteritinib 120 mg daily vs investigator's choice (fludarabine-cytarabine-filgrastim-idarubicin; mitoxantrone, etoposide, and cytarabine; azacitidine; or LDAC).[27] Complete responses were higher for gilteritinib than standard care (CR/CRi 34% vs 15.3% and CR 21% vs 11%), which translated into significantly improved OS (median, 9.3 vs 5.6 months). Furthermore, among patients with hematologic response, gilteritinib induced a molecular response (variant allele frequency [VAF] $\leq 10^{-2}$) using a next-generation sequencing (NGS)-based FLT3-ITD–specific assay in 25% of evaluable cases. FLT3-ITD detection by capillary electrophoresis, as used in many laboratories, has a similar threshold of detection.[29] In our case, the patient relapsed after prior midostaurin exposure. As only 13% of patients in the ADMIRAL study recorded prior exposure to FLT3 inhibitors, future studies are needed to verify the activity of second-line gilteritinib in this setting.

Trials of intensive 7 + 3-based chemotherapy with second-generation FLT3 inhibitors including crenolanib, gilteritinib, and quizartinib are ongoing, with high response rates (CR/CRi ≥ 84%) typically observed in newly diagnosed patients with FLT3-ITD mutation.[30-32] It remains to be demonstrated whether FLT3 inhibitor-chemotherapy combinations will be similarly effective in the salvage setting, where elevated levels of FLT3 ligand, thought to antagonize the activity of FLT3 inhibitors, are more prevalent.[33] Preliminary data suggest that gilteritinib in combination with azacitidine may have potential in the relapsed/refractory (R/R) setting.[34] Although our case responded to gilteritinib monotherapy, combination with azacitidine in resistant FLT3-mutant cases has logical appeal, especially to mitigate against the risk of emergent drug resistance (eg, RAS mut) reported with gilteritinib monotherapy.[35]

There is growing interest in continuing FLT3 inhibitors as maintenance therapy, particularly post-HSCT. In both of the QuANTUM-R and ADMIRAL studies, posttransplant maintenance was allowed and outcomes appeared best if maintenance FLT3 inhibitor was continued in the posttransplant setting; although, in both studies, this was not subject to a second randomization. An ongoing randomized trial (BMT CTN 1506) will determine the effectiveness of gilteritinib in the post-HSCT setting. We recommend that FLT3 inhibitors be restarted as early as 30 days post-HSCT, once engraftment has occurred and in the absence of clinically significant GVHD, infection, or other toxicity. Preclinical studies suggest that the FLT3 inhibitor sorafenib induces interleukin 15 production from FLT3-ITD cells in the postallograft setting, enhancing effector T-cell graft-versus-leukemia activity.[36] In support of this concept, a phase 2 randomized study in FLT3-ITD AML showed improved relapse-free survival with sorafenib vs placebo maintenance after HSCT (2-year relapse-free survival, 85% vs 53%; hazard ratio, 0.39; $P = .013$),[37] suggesting post-HSCT sorafenib may have utility in the post-HSCT maintenance setting. In our patient, we elected to use gilteritinib as maintenance therapy post-HSCT given his excellent response and tolerability to gilteritinib as first salvage therapy and in accord with practice in the ADMIRAL study. A number of treatment-related complications may occur with gilteritinib and the physician should be vigilant in monitoring and managing these side effects (Table 5).

Patient 3: an older woman with relapsed IDH1-mutant AML

A 78-year-old woman was noted to have a history of cytopenias 2 years prior to her current presentation for elective orthopedic surgery. Her blood work revealed a WBC of 2.3×10^9/L with 12% blasts; hemoglobin was 8.6 g/dL, neutrophils were 0.3×10^9/L, and platelets were 114×10^9/L. Bone marrow examination confirmed AML with 28% myeloblasts and trisomy 8 on cytogenetic analysis. A molecular panel was not performed at the time and she received azacitidine as initial therapy (venetoclax was not available). After 3 cycles, hematologic improvement was noted, and a subsequent bone marrow after 5 cycles confirmed

Table 5. Summary of our recommendations for gilteritinib administration

Issue	Management
Target drug dose	Gilteritinib: 120 mg orally once daily with or without food The estimated half-life of gilteritinib is 113 h
Optimize dosing	P-gp and strong CYP3A inducers may decrease gilteritinib exposure Strong CYP3A inhibitors may increase gilteritinib exposure (Cmax increased ~20% and AUC increased ~120%) but gilteritinib dose adjustment is not required Gilteritinib may reduce the effects of drugs that target the 5HT2B receptor or the σ nonspecific receptor (eg, escitalopram, fluoxetine, sertraline)
Monitoring and management of DS	Patients treated with gilteritinib may develop differentiation syndrome, which can be fatal or life-threatening if not treated Of 319 patients, 3% experienced DS, which occurred as early as 2 days and up to 75 days after gilteritinib initiation and has been observed with or without concomitant leukocytosis; full blood count and biochemical monitoring is recommended 1-2× weekly for at least the first month of therapy If DS is suspected, initiate dexamethasone 10 mg postoperatively/IV every 12 h and taper after a minimum of 3 days if resolution of symptoms; DS may recur with premature discontinuation of corticosteroid treatment; if severe signs and/or symptoms persist for >48 h after initiation of corticosteroids, interrupt gilteritinib until signs and symptoms improve
Hepatic impairment	If ALT and/or AST >5× ULN (or >3× ULN with elevation of total bilirubin), interrupt gilteritinib until improvement to grade ≤1; restart gilteritinib at 80 mg daily
Pancreatitis	Lipase elevation reported in 4% Interrupt gilteritinib until pancreatitis is resolved; resume gilteritinib at 80 mg
PRES	1% experienced PRES[63] with symptoms including seizure and altered mental status; symptoms have resolved after discontinuation of gilteritinib Discontinue gilteritinib in patients who develop PRES
Monitoring for prolonged QT syndrome	7% have an increase from baseline QTc >60 ms; prolonged interval >500 ms is rare (1%); if QTcF >500 ms, interrupt gilteritinib and resume at 80 mg when QTc interval returns to ≤480 ms; substitute QT prolonging with non-QT prolonging coadministered drugs if possible
Patients with renal impairment	Mild or moderate renal impairment does not affect gilteritinib
When to cease therapy?	Median time to first response was 1.8 mo and 3.6 mo to CR As response may be delayed, in the absence of disease progression or unacceptable toxicity, treatment of a minimum of 6 mo is recommended to allow time for a clinical response
Assessment for drug resistance mutations at disease progression	Mutations in the RAS/MAPK signaling pathway (N/KRAS, PTPN11), FLT3-F691L gatekeeper mutations or BCR-ABL1 fusions[35]

AUC, area under the curve; Cmax, maximum or peak concentration; DS, differentiation syndrome; P-gp, P-glycoprotein; PRES, posterior reversible encephalopathy syndrome.

CR. After 9 cycles of therapy, progressive cytopenias were noted and a bone marrow demonstrated relapsed AML with 37% blasts and recurrence of trisomy 8. An AML NGS panel identified DNMT3A-R882 (VAF, 40%) and IDH1-R132C (VAF, 35%) mutations.

Question Should this patient with HMA failure receive chemotherapy or ivosidenib salvage?

Proposed treatment

We propose that this patient should receive ivosidenib. She was initiated on ivosidenib 500 mg orally daily. An electrocardiogram prior to treatment initiation demonstrated a corrected QT (QTc) of 450 ms. Two weeks into therapy, her QTc increased to 475 ms. Concurrent use of prophylactic fluoroquinolone was changed to a cephalosporin and the QTc interval returned to baseline. Four weeks into therapy, the WBC increased to 8×10^9/L with 45% neutrophils, 10% metamyelocytes, 7% monocytes, and 5% blasts. At 6 weeks, her WBC increased to 27×10^9/L with a similar differential. She complained of shortness of breath with peripheral leg edema. A chest radiograph demonstrated bilateral infiltrates, with oxygen saturation 94% and fever (38.8°C). Hydroxycarbamide was commenced and she was admitted and started on broad-spectrum antibiotics, furosemide, and dexamethasone 10 mg twice daily for suspected differentiation syndrome. Ivosidenib was continued. Her symptoms improved swiftly. The microbiological workup was negative and an echocardiogram ruled out pericardial effusion or impaired ejection fraction. She was discharged on a 2-week steroid taper. Hydroxycarbamide was ceased when the WBC fell to $<20 \times 10^9$/L. After 3 months of therapy, blood counts were normal and a repeat marrow assessment showed 3% blasts, consistent with CR. IDH1mut remained detectable by NGS and digital PCR. At 6 months, IDH1mut was negative by NGS (sensitivity 2%), with IDH1mut still positive by digital PCR. The patient was alive and in ongoing remission at the time of last follow-up, 12 months from ivosidenib initiation.

Comments

Salvage therapies after HMA failure Secondary AML evolving from treated prior antecedent hematologic disease, recently

Table 6. Summary of our recommendations for ivosidenib and enasidenib administration

Issue	Ivosidenib	Enasidenib
Target drug doses	Ivosidenib: 500 mg orally once daily with or without food Levels will be increased by high-fat meals; the drug has a terminal half-life of 94 h	Enasidenib: 100 mg orally once daily with or without food The drug has a terminal half-life of 137 h
Optimize dosing	Ivosidenib is primarily metabolized by CYP3A4 Therefore, CYP3A4 inhibitors will increase ivosidenib levels, which could prolong QTc interval If a strong CYP3A4 inhibitor is used, monitor for increased risk of QTc interval prolongation	Not applicable
Monitoring and management of DS	IDH inhibitors can induce myeloid proliferation resulting in IDH-DS Assess blood counts and chemistries at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy If differentiation syndrome is suspected • Initiate dexamethasone 10 mg IV or orally every 12 h • Commence hydroxyurea if concomitant noninfectious leukocytosis • Continue for a minimum of 3 days and taper if symptoms improve • Interrupt IDH inhibitor if severe cardiopulmonary symptoms, requirement of hospitalization, and/or renal dysfunction persists for >48 h after initiation of corticosteroids	
Noninfectious leukocytosis WBC >25 × 10^9/L or an absolute increase in WBC >15 × 10^9/L from baseline	Initiate treatment with hydroxyurea Interrupt IDH inhibitor if leukocytosis not improved with hydroxyurea Resume IDH inhibitor at target dose after resolution	
Isolated elevated indirect BR ≥3× ULN	Not applicable	Enasidenib may interfere with bilirubin metabolism through inhibition of UGT1A1 Bilirubin elevations ≥2× ULN may occur in 37%, most commonly within the first month of treatment Reduce enasidenib to 50 mg daily and resume back at 100 mg when BR ≤2× ULN
Monitoring for prolonged QT syndrome	If concomitant use of drugs known to prolong the QTc interval (eg, antiarrhythmic medicines, fluoroquinolones, triazole antifungals, 5-HT3 receptor antagonists) cannot be avoided, monitor EKG's at least weekly for the first 3 wk of therapy then intermittently thereafter If QTc interval >450 ms: correct electrolytes and modify concomitant drugs known to prolong QTc If QTc interval >480 ms: interrupt ivosidenib until QTc ≤480 ms and then resume at 500 mg daily If QTc interval prolongation associated with life-threatening arrhythmia, discontinue ivosidenib permanently	Not applicable
Patients with hepatic impairment	No modification of the starting dose is recommended for patients with mild or moderate (Child-Pugh A or B) hepatic impairment; the pharmacokinetics and safety in patients with severe hepatic impairment (Child-Pugh C) are unknown	
Patients with renal impairment	No modification of the starting dose is recommended for patients with mild or moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2); the pharmacokinetics and safety in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) are unknown	
When to cease therapy?	Ivosidenib: the median time to CR or CRh was 2.8 mo with 92% achieving a first response within 6 mo of initiating therapy If there has not been a meaningful blast reduction or hematologic response after 6 cycles of therapy, consider ceasing treatment if effective alternate options exist	Enasidenib: the median time to CR or CRh was 1.9 mo with 85% achieving a first response within 6 mo of initiating therapy If there has not been a meaningful blast reduction or hematologic response after 6 cycles of therapy, consider ceasing treatment if effective alternate options exist

2-HG, 2-hydroxyglutarate; BR, bilirubin; EKG, electrocardiogram; GBS, Guillain-Barré syndrome.

Table 6. (continued)

Issue	Ivosidenib	Enasidenib
GBS	<1% (2 of 258) in the clinical study developed GBS Monitor for new signs or symptoms of motor and/or sensory neuropathy, paresthesias, or difficulty breathing Permanently discontinue ivosidenib in patients diagnosed with GBS	Not applicable
Monitoring for drug resistance mutations at disease progression	Off-target resistance: mutations in K/NRAS, RUNX1[64,65] On-target resistance: loss of 2-HG suppression associated with second site mutations in IDH[66]	

2-HG, 2-hydroxyglutarate; BR, bilirubin; EKG, electrocardiogram; GBS, Guillain-Barré syndrome.

coined as "treated secondary AML" in the context of HMA failure is known to be a highly challenging scenario, with a median OS <5 months.[38,39] In fitter patients with AML, intensive chemotherapy for patients with HMA failure is associated with a response rate of 32% and median OS of 6.2 months.[40] Outcomes for patients with de novo AML refractory to or relapsing after HMA therapy are also very poor, with survival expectations ranging between 2 and 4 months.[41] Therefore, novel therapies are urgently needed for patients with AML in the context of HMA failure.

Molecular rescreening is important for older patients with HMA failure to enable identification of actionable mutations. This is especially warranted as IDH mutations occur with higher frequency in patients >60 years of age (IDH1mut, 9% to 13%; IDH2mut, 15% to 16%).[3,42] As in our patient, a preserved platelet count is often seen in patients with IDHmut AML.[43] Orally administered, small molecule–targeted inhibitors of mutant IDH1 (ivosidenib) and IDH2 (enasidenib) target mutant IDH enzymes and block production of the 2-hydroxyglutarate oncometabolite. Overall responses with ivosidenib and enasidenib are described in ~29% to 34% of patients, including CR in 20% to 22% of enrolled patients in phase 1-2 trials with median OS of ~9 months for patients with R/R disease (Table 3). For ivosidenib, higher CR plus CRh (platelets, $>50 \times 10^9$/L; neutrophils, $>0.5 \times 10^9$/L) responses were observed in patients failing 1 prior regimen, compared with more advanced patients receiving ≥3 prior regimens (46% vs 15%).[44] For responders to ivosidenib, 50% of patients treated with R/R disease were still alive at 18 months. Furthermore, deep IDH1 mutation clearance was achieved in 21% of responding patients, indicating the potential for IDH-targeted therapy to modify the natural history of the disease.

Echoing the discussion of case 2, the current recommended treatment approach is IDH inhibitor monotherapy. However, several ongoing clinical trials are testing the utility of IDH inhibitors in various combinations (with intensive chemotherapy, azacitidine, or venetoclax) and we suspect that the use of IDH inhibitors in these potentially more effective combinations will likely become the preferred option in the near future. Notably, preliminary results with ivosidenib plus azacitidine in previously untreated patients report that CR was achieved in 9 of 13 (69%), associated with IDH1 mutation clearance.[45] Furthermore, ivosidenib plus venetoclax in the absence of chemotherapy demonstrated a CR/CRi rate of 75%.[46] Further mature results with these promising regimens are anticipated.

Managing IDH inhibitor complications Although both ivosidenib and enasidenib are well-tolerated oral agents, each drug has a distinct toxicity profile (Table 6). With ivosidenib, QTc prolongation (>450 ms) occurs in 25% of patients, including grade 3 or higher events (>500 ms) in 10%.[44] Notably, this study did not prohibit use of concomitant QTc-prolonging agents such as antiemetics, antibiotics, or antifungals, and discontinuation of concomitant QTc-prolonging agents and repletion of electrolytes (potassium, magnesium) may be sufficient for resolution. Enasidenib is metabolized by UGT1A1 and ~35% of patients receiving enasidenib will develop indirect hyperbilirubinemia analogous to Gilbert syndrome. In most cases, this problem is self-limiting and no interventions are required. Dose interruptions, however, are justified in the setting of clinically significant jaundice.

As IDH inhibitors function by restoring myeloid differentiation, their use may lead to robust myeloid maturation and proliferation, which in turn may lead to the development of an IDH inhibitor "differentiation syndrome" (DS).[47] Similar to DS in APL, IDH-DS often occurs during the initial period of myeloid maturation with a median time of onset 29 days (range, 5-59 days) after commencing therapy. Later-onset DS may occur if therapy is interrupted and restarted. IDH-DS is a nonspecific syndrome manifesting as dyspnea, culture-negative fever, pulmonary infiltrates, hypoxia, pleural or pericardial effusions, peripheral edema, and weight gain. Due to the nonspecific symptomatology, clinician awareness is necessary as these symptoms often overlap with infections and/or progressive AML. IDH-DS is reported in ~15% of patients treated across IDH inhibitor studies and may co-occur with hyperleukocytosis. If IDH-DS is clinically suspected, corticosteroids should be promptly initiated with 10 mg of dexamethasone twice daily for at least 3 days or until improvement. Hydroxycarbamide may be required for concomitant hyperleukocytosis, and patients should be monitored for TLS. It is important to note that due to the long half-life of IDH inhibitors (exceeding 4 days), treatment interruption is not likely to result in rapid resolution of symptoms. However, for patients with progressive hypoxia, renal failure, leukocytosis, disseminated intravascular coagulation, or other medical emergencies, interruption of IDH inhibitor administration is appropriate.

Conclusions

The treatment landscape of AML is undergoing unprecedented change, with no fewer than 8 new drug approvals since 2017. Our treatment paradigm has shifted away from a simple binary distinction between "curative, intensive therapy" and "palliative, lower intensity" approaches. Instead, the increased diversity of

therapeutic options requires a more nuanced treatment algorithm that incorporates mutation-specific targeted therapies, monoclonal antibodies, and apoptosis-inducing small molecules, in addition to improved liposomal delivery of standard therapies. We fully expect and sincerely hope that our review of "new drugs" will be antiquated in the next few years due to the rapid pace of clinical development and abundance of newly approved therapies. We highlight caution, however, in unrestrained combination of these new drugs outside of the context of clinical trials, as prevention of unanticipated severe drug-induced toxicities is imperative. Carefully conducted clinical studies that report on the safety of new combinations, supported by correlative studies illuminating mechanisms of response and resistance, will be critical to ensure that future progress is safe for patients and supported by a strong body of scientific evidence.

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Footnotes

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