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Intensive Versus Non-intensive Therapy for Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

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Introduction

Newly approved treatments have increased the options available for patients with acute myeloid leukemia (AML), but have also generated questions concerning the selection of the most appropriate therapy for a given individual (**Tables 1 & 2**).[1-13] The trials leading to the approval of these therapies were based on limited genetic data (e.g., cytogenetics, *FMS-like tyrosine kinase-3 [FLT3]* status) and clinical parameters (e.g., age, comorbidities, therapy, or secondary AML). Data concerning effectiveness or lack of efficacy of a drug or drug regimen in specific AML subgroups is often determined after drug approval. For example, venetoclax (VEN) + azacitidine (AZA) lower intensity therapy (LIT), which is approved for the treatment of patients with newly diagnosed AML deemed ineligible for intensive chemotherapy (IC) or aged >75 years, was found to have limited efficacy in patients with mutated *TP53*.[14,15] Despite the regulatory approved indications for VEN-based LIT, some older and younger patients can be selected for either LIT or IC. Furthermore, with the availability of maintenance therapy after IC16,

several important questions have emerged regarding the role of IC in older patients.

No published prospective studies have compared IC with LIT in "fit" patients with newly diagnosed AML to inform treatment choice. Two retrospective propensity score matched real-world data analyses of outcomes in patients with newly diagnosed AML (irrespective of the genetic profile) who received induction with VEN + AZA or IC, indicated no difference in overall survival (OS).[17,18] However, one study showed improved complete remission (CR) and/or allogeneic hematopoietic stem cell transplant (alloHCT) rates in favour of IC (60.9% vs. 44.2%, *P* = 0.006 and 18.1% vs. 8.0%, *P* = 0.012, respectively).[17] Other single-centre retrospective studies comparing VEN + AZA with IC have yielded conflicting results.[19,20] None of these studies provided information concerning the use of oral AZA maintenance therapy. The studies did suggest that outcomes may be dependent on specific genetic abnormalities and/or clinical factors.[17,19,20] Currently, several Phase 2 trials are comparing VEN + AZA with IC in adult patients with newly diagnosed AML (NCT04801797, NCT05904106, NCT05554406, NCT05554393).

Here, two case scenarios will be discussed to highlight issues surrounding treatment choice: **a)** fit individuals who are ≥75 years with newly diagnosed European LeukemiaNet (ELN)-defined favourable-risk AML and **b)** IC eligible persons who are ≥18 years with newly diagnosed ELN-defined poor-risk AML, who require alloHCT in first complete remission (CR1) with curative intent.

Case 1

A 75-year-old woman with a history of type 2 diabetes mellitus, hypertension, and dyslipidemia presented with a white blood cell count (WBC) of 66.7 × 10^9/L, 2.27 × 10^9/L neutrophils, and 103 × 10^9/L platelets, with 27% circulating blasts. The diagnostic workup showed 84% marrow myeloblasts expressing CD33, CD45, CD117, CD123, and myeloperoxidase (MPO). Cytogenetics revealed a normal karyotype in all 20 metaphases. Rapid molecular testing identified an *NPM1* mutation and the absence of *FLT3* internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutations. Results from a next-generation sequencing (NGS)-based gene panel would not be available for another 2 weeks. This was consistent with a presumptive diagnosis of AML with mutated *NPM1*,[21,22] pending additional genetic results. Her Eastern Cooperative Oncology Group (ECOG) performance status was 1. The patient received cytoreductive hydroxyurea and allopurinol. Should she receive IC or LIT with VEN + AZA?

What are the Outcomes with IC Followed by Oral AZA Maintenance Treatment Compared with VEN + AZA in Older Patients with *NPM1*-mutated AML?

Approximately 30% of AML cases harbor *NPM1* mutations.[23] In both the ELN 2022 genetic risk classification, which was developed predominantly from younger patients receiving IC, and the newer ELN 2024 genetic risk classification for LIT, the presence of an *NPM1* mutation is considered favourable in the absence of adverse cytogenetics and *FLT3*-ITD mutation or absence of signalling mutations.[24,25] However, *NPM1*-mutated AML remains a very heterogenous disease with outcomes dependent not only on the presence of co-occurring genetic abnormalities (e.g., *FLT3*-ITD, *DNMT3A*, *WT1*), but also on clinical parameters (e.g., age and WBC at presentation), type of *NPM1* mutation, and measurable residual disease (MRD) status.[23,26]

Two retrospective studies compared IC with VEN + a hypomethylating agent (HMA) in older patients with *NPM1*-mutated AML.[27,28] In multivariate analysis, no statistically significant difference in OS was found between the two groups; however, information on the use of oral AZA maintenance therapy, subsequent lines of therapy, and MRD status were not available. One-study suggested that patients with *NPM1*-mutated AML with normal cytogenetics and without *FLT3*-ITD mutation may benefit from IC over VEN + HMA.[28]

IC Followed by Oral AZA Maintenance

Swedish registry data showed that 66.4%, 44.5%, and 22.9% of patients aged 70–74 years, 75–79 years, and 80–84 years, respectively, can be considered fit for IC.[29] Early deaths in older individuals (i.e., ≥60 years) treated with IC varied from 6% to 12% in randomized trials(**Table 1**),[1,2,30] whereas retrospective data from European registries have documented a 30-day mortality of 13%.[31]

A median OS of ~42 months or a 2-year OS of ~56% can be achieved in older patients with *NPM1*-mutated AML who received IC.[32-34] Up to 80% of patients with *NPM1*-mutated AML can achieve NPM1 MRD negativity after 2 cycles of IC, which is associated with improved

	CPX-351[¶], [1,2,20,71] (*N = 153*)	GO[§] + 3+7[3,4] (*N = 139*)	Midostaurin[¥] + 3+7[6,7] (*N = 360*)	Quizartinib[‡] + 3+7[8] (*N = 268*)
Characteristics				
Median age, y (range) Age >75 y	67.8[a] Not provided but no patients >75 y	62.8 (59.3–66.8)b 0[c]	48.6 (18–60.9)d 0[c]	56 (23–75)[e] Not provided but no patients >75 y
***De novo* AML**	41 (26.8%)	139 (100%)	---	243 (91%)
Therapy-related AML (tAML)	30 (19.6%)	0[c]	0[c]	0[c]
Secondary AML (sAML)	82 (53.6%)	0[c]	---	25 (9%)
Cytogenetic risk group Good Intermediate Poor	 7 (4.9%) 64 (44.8%) 72 (50.3%)	 3 (2%) 91 (65%) 28 (20%)[d]	 16/269 (5.9%) 231/269 (85.9%) 22/269 (8.2%)	 14 (5%) 197 (74%) 19 (7%)
Gene mutations *FLT3-ITD/TKD* *TP53*	 22/138 (15.9%) 24 (15.6%)	 *FLT3-ITD* 22/137 (16%) ---	 *FLT3-ITD* 279 (77.5%) / *FLT3-TKD* 81 (22.5%) ---	 *FLT3-ITD* 268 (100%) ---
Outcomes				
CR + CRi All tAML sAML Poor-risk cytogenetics FLT3-ITD/TKD *TP53*	 73 (47.7%; CR 37.3%) 14/30 (46.7%; CR 36.7%) 36/82 (43.9%: CR 32.9%) 31/72 (43.1%; CR 34.7%) 15/22 (68.2%; CR 54.5%) 7/24 (CR 29.1%)	 CR + CRp 113 (81%; CR 73%) ---[c] ---[c] 14/28 (50%; CR not provided) FLT3-ITD 21/22 (95.5%; CR not provided) Not done	 CR 212/360 (59%); expanded CR 244/360 (68%) ---[c] --- --- CR 212/360 (59%); expanded CR 244/360 (68%) ---	 192 (72%; CR 54.9%) ---[c] --- --- FLT3-ITD 192 (72%; CR 54.9%) ---

	CPX-351¶, [1,2,20,71] (*N = 153*)	GO§ + 3+7[3,4] (*N = 139*)	Midostaurin¥ + 3+7[6,7] (*N = 360*)	Quizartinib‡ + 3+7[8] (*N = 268*)
Median duration of response, mos (95% CI)	6.93	---	---	38.6 (21.9-not estimable)
Median follow-up, mos	60.9	47.6	59	39.2
Median OS, mos (95% CI)	9.33 (6.37–11.86)	27.5 (21.4–45.6)	74.7 (31.5-not reached)	31.9 (21-not estimable)
Poor-risk	6.42 (4.96–9.66)	---	---	Not reached
cytogenetics	10.25 (5.62–14.95)	---	---	FLT3-ITD 31.9 (21-not estimable)
FLT3-ITD/TKD	4.5 (2.9–7.6)	---	---	---
TP53				
OS, % (95% CI)	18 (12-25) at 5y	---	43.7 (38.7-49.3) at 10y	---
30-day mortality	5.9%	3.8%	---	6%

Table 1. Front-line Phase 3 Randomized Clinical Trials with Intensive Chemotherapy (IC); *modified from Tang et al.*

¶ Approved for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
§ Approved for the treatment of newly-diagnosed CD33-positive AML in adults in combination with daunorubicin and cytarabine for adults with newly-diagnosed AML, except acute promyelocytic leukemia (APL).
¥ Approved for use with standard cytarabine and daunorubicin induction and cytarabine consolidation for the treatment of adults with newly diagnosed *FLT3*-mutated AML.
‡ Under Health Canada review for regulatory approval for use with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML that is *FLT3*-ITD-positive.

[a] Eligible age for enrolment onto study: 60–75 y.
[b] Eligible age for enrolment onto study: 50–70 y.
[c] This group of patients were not eligible for the study.
[d] Cytogenetics not available in 17 patients (12%); [d] eligible age for enrolment onto study: 18–<60 y.
[e] Eligible age for enrolment onto study: 18–75 y.

Abbreviations: 3+7: daunorubicin (or idarubicin) + cytarabine; **AML:** acute myeloid leukemia; **CI:** confidence interval; **CR:** complete remission; **CRp:** CR with incomplete platelet recovery; **CRi:** complete remission with incomplete count recovery; **GO:** gemtuzumab ozogamicin; **mos:** months; **OS:** overall survival; **y:** years

	VEN + AZA[¶] [9,10] (*N = 286*)	VEN + LDAC[§] [11,12] (*N = 143*)	AZA + ivosidenib[¥] [13] (*N = 72*)
Characteristics			
Median age, y (range)	76 (59–91)	76 (36–93)	76 (58–84)
Age >75 y	174 (61%)	82 (57%)	39 (54%)
***De novo* AML**	214 (75%)	85 (59%)	54 (75)
Therapy-related AML (tAML)	26 (9%)	6/58 (10%)	2 (3%)
Secondary AML (sAML)	46 (16%)	52/58 (90%)	16 (22%)
Prior HMA	0[a]	28 (20%)	0[a]
Cytogenetic risk group			
Good	0[a]	1 (1%)	3 (4%)
Intermediate	182 (64%)	90 (63%)	48 (67%)
Poor	104 (36%)	47 (33%)	16 (22%)
Gene mutations			
FLT3-ITD/TKD	29/206 (14%)	20/112 (18%)	4/58 (7%)
IDH1/2	61/245 (25%)	21/112 (19%)	*IDH1 72* (100%)
TP53	38/163 (23%)	22/112 (20%)	5/58 (9%)
Outcomes			
CR + CRi			
All	191 (66.8%; CR 36.7%)	69 (48%; CR 27%)	39 (54%; CR 47%)[c]
tAML	s/tAML 48/72 (66.7%)	s/tAML 21/58 (36%; CR 16%)	---
sAML			---
Poor-risk cytogenetics	55/104 (52.9%)	13/47 (28%; CR 17%)	---
Prior HMA	---[a]	7/28 (25%; CR 7%)	---[a]
FLT3-ITD/TKD	21/29 (72.4%)	9/20 (45%; CR25%)	---
IDH1/2	47/63 (74.6%)[b]	12/21 (57%; CR 38%)	39 (54%; CR 47%) for *IDH1*
TP53	21/38 (55.3%)	4/22 (18%; CR 5%)	---

	VEN + AZA[¶] [9,10] (*N = 286*)	VEN + LDAC[§] [11,12] (*N = 143*)	AZA + ivosidenib[¥] [13] (*N = 72*)
Time to response, mos (range)	1.3 (0.6–9.9) for CR + CRi	Before initiation cycle 2: 34% for CR + CRi	2.1 (1.7–7.5)
Median duration of response, mos (95% CI)	18.2 (13.6–23.1) for CR + CRi	11.7 for CR + CRi	22.1 (13-not estimable)
Median follow-up, mos	43.2	17.5	12.4
Median OS, mos (95% CI)	14.7 (12.1–18.7)		
Poor-risk cytogenetics	---	8.4 (5.9–10.1)	24 (11.3–34.1)
Prior HMA	---[a]	4.4 (3–6.4)	---
IDH1/2	19.9 (12.2-27.7)/IDH1 10.2 (2.3-25.1)	5.6 (3.4–9.6) ---	---[a] IDH1 24 (11.3–34.1)
OS, % (95% CI)	37.5 (31.8-43.3) at 2 y	---	---
30-day mortality	21/286 (7%)	18/143 (13%)	---

Table 2. Front-line Phase 3 Randomized Clinical Trials with Lower Intensity Therapy (LIT) for Patients Ineligible for Intensive Chemotherapy (IC) or age >75 y; *modified from Tang et al.*

[¶] approved for the administration of venetoclax in combination with AZA for the treatment of newly-diagnosed AML in adults who are >75 years, or who have comorbidities that preclude use of intensive induction chemotherapy.
[§] approved for the administration of venetoclax in combination with LDAC for the treatment of newly-diagnosed AML in adults who are >75 years, or who have comorbidities that preclude use of intensive induction chemotherapy.
[¥] approved for the administration of ivosidenib in combination with AZA for the treatment of adult patients with newly diagnosed AML with an *IDH1* R132 mutation who are not eligible for intensive induction chemotherapy

[a] this group of patients were not eligible for the study.
[b] CR + CRi for *IDH1* mutated 13/23 (56.5%) and for *IDH2* mutated 34/40 (85%).
[c] response by 24 weeks

Abbrviations: AZA: azacitidine; **CI:** confidence interval; **CR:** complete remission; **CRh:** CR with hematologic improvement; **CRi:** complete remission with incomplete count recovery; **HMA:** hypomethylating agent; **LDAC:** low-dose cytarabine; **MDS:** myelodysplastic syndrome; **mos**: months; **NR:** not reached; **ORR:** overall response rate (CR + CRi + morphologic leukemic-free state [MLFS]); **OS:** overall survival; **y:** year

OS with a lower risk of relapse.[26] Induction chemotherapy is typically followed by 2 to 4 cycles of consolidation therapy depending on the treatment regimen.[16,24,35,36] Oral AZA maintenance therapy for older patients with AML with intermediate-or poor-risk cytogenetics in CR1 after IC has been shown to improve survival (from the time of randomization) compared to placebo (i.e., 24.7 months vs. 14.9 months, respectively; *P* <0.001) with estimated 3-year and 5-year OS rates of 37.4% and 26.5% compared to 27.9% and 20.1%, respectively.[16,36] Treatment with oral AZA also resulted in a higher conversion from MRD positive status (as measured by multiparameter flow cytometry [MFC]) at baseline to MRD negative status during treatment compared with placebo (37% vs. 19%; odds ratio: 2.50 [95% confidence interval [CI]: 1.35–4.61]).[37] Retrospective analysis involving 99.4% of participants who had mutational data available at the time of AML diagnosis revealed that patients with *NPM1*-mutated AML in CR1 with or without MRD negativity by MFC who received oral AZA maintenance had a median OS of 48.6 months and 46.1 months, respectively (compared with 31.4 months and 10 months, respectively, in the placebo arm).[38]

Is There Any Benefit for Administering Gemtuzumab Ozogamicin (GO) with IC in Patients with NPM1-mutated AML?

GO is approved in combination with daunorubicin and cytarabine (3+7) in the treatment of patients with newly diagnosed CD33-positive AML with favourable or intermediate-risk cytogenetics (**Table 1**). Administration of GO with IC in patients with newly diagnosed *NPM1*-mutated AML is associated with increased MRD negativity and decreased risk of relapse; however, this has not been shown to lead to improved event-free survival (EFS) or OS, potentially due to increased early death rates in participants >70 years of age who received GO.[33,39,40]

LIT with VEN + AZA

Lower intensity VEN-based regimens (i.e. VEN + AZA or VEN + LDAC) are associated with early death rates of 7–13% (**Table 2**).[9-12] Treatment with VEN + AZA in IC-ineligible patients with newly diagnosed AML yielded a median OS of 14.7 months with an estimated 2-year OS of 37.5%.[9,10] However, patients with *NPM1*-mutated AML without signalling mutations (i.e., absence of *FLT3-ITD, KRAS, NRAS*, and *TP53* mutations) had a median OS of 39 months.[41]

Up to 42% of patients can achieve MRD negativity by MFC during the course of treatment with VEN + AZA; however, only 21% achieved MRD negativity after 4 cycles of therapy in this study.[42] Achievement of *NPM1* MRD negativity after 4–6 cycles of VEN-based LIT has been associated with improved OS.[26,43] Although achievement of an MRD negative CR after IC is associated with improved OS and relapse-free survival (RFS), the role of MRD in patients receiving LIT requires further evaluation.[42,44,45] Treatment with VEN-based LIT is long-term and continues until signs of disease progression, unacceptable toxicity, or patient request.[9,11] Most patients require VEN dose modifications to manage cytopenias without adversely affecting survival.[46] Among the 68% VEN + AZA-treated patients who achieved a CR or CR with incomplete count recovery (CRi), the median number of treatment cycles was 13 (range: 1–46), with 76% of patients receiving ≥6 cycles. The number of cycles that patients with *NPM1*-mutated AML received was not specified. A small number of patients in CR have discontinued VEN-based LIT with a median treatment-free survival of 16 to 46 months.[26,47,48]

Is the Quality of Life (QoL) Impacted in Patients Receiving IC Followed by Oral AZA Maintenance or with VEN + AZA?

IC is administered for a limited treatment period and is associated with short-term toxicities.[49,50] QoL improves during treatment (i.e., from induction to consolidation chemotherapy), independent of age.[49,50] Oral AZA maintenance chemotherapy is easy to administer, convenient for both patients and caregivers, results in fewer clinic or hospital visits, and abrogates injection site reactions without decreasing favourable health-related QoL for patients with AML in CR (compared to placebo).[16,51]

In contrast, treatment with VEN + AZA is prolonged, increases caregiver burden, and requires multidisciplinary care, serial visits to the hospital or clinic for AZA injections, and several VEN dose and/or cycle adjustments to allow for count recovery.[10] QoL assessments were similar between VEN + AZA vs. placebo + AZA (*P* = 0.65,) and there was a trend of longer time to deterioration in global health score in the VEN + AZA arm compared to placebo + AZA.[10] Obviously, no QoL assessments comparing VEN + AZA to placebo alone has been performed.

Case 1 Patient Update

The patient from case 1 received IC with 3+7 (i.e., daunorubicin 60 mg/m^2/d and cytarabine 100 mg/m2d),[35,53] without the addition of GO. Her course in hospital was complicated by proctocolitis, bacteremia in the setting of line-associated thrombosis in the left basilic vein, and the development of platelet alloantibodies. She achieved a CR with MRD negativity by both MFC and molecular analysis, with undetectable *NPM1* transcripts after 1 cycle of induction chemotherapy. During this interval, NGS at diagnosis was reported and revealed the presence of pathogenic Type A *NPM1* c.860_863dupTCTG p.(Trp288fs) and TET2 c.4082delG p.(Gly1361fs) variants. Hence, the only adverse features associated with *NPM1*-mutated AML were her increased age and elevated WBC at presentation. She completed outpatient consolidation therapies with an end-of-treatment bone marrow (BM) showing an ongoing morphological remission with both MFC and *NPM1* MRD negativity. The patient started maintenance therapy with oral AZA with serial BM assessments to monitor the MRD status.

What is the Role of Serial MRD Assessment?

Despite achieving *NPM1* MRD negativity after IC, patients remain at a relapse risk of 22% to 40% at 3 years.[26,53] The benefit of oral AZA maintenance was observed irrespective of MRD status at baseline, with improved OS in those who were MRD negative.[36,37] The patient had serial BM analyses performed every 3 months for *NPM1* MRD assessments,[54] as documentation of a molecular relapse will lead to hematological relapse without therapeutic intervention.[53,55] She has been receiving oral AZA maintenance therapy for 17 months with ongoing *NPM1* MRD negativity.

What is the Duration of Maintenance Therapy with Oral AZA?

There is a lack of data, including the use of MRD, to help guide decisions concerning when to discontinue oral AZA maintenance therapy. In the Quazar AML-001 trial, oral AZA maintenance was administered until patients were no longer deriving benefit.[16,36] At 55.5 months of follow-up, only 11% of patients were still receiving oral AZA maintenance. Overall, 23% of patients had received ≥36 treatment cycles (~3 years) and 14% received ≥60 cycles.

Case 2

A 58-year-old man with a prior history of treated diffuse large B-cell lymphoma presented to the local emergency department with a temperature of 38.6°C, coughing, and rhinorrhea. A CT scan of the chest demonstrated left lower lobe pneumonia. Blood cultures were negative for bacterial growth. Bloodwork revealed WBC: 0.8 × 10^9/L, neutrophils: 0.2 × 10^9/L, platelets: 47 × 10^9/L, with rare circulating blasts. BM aspirate and biopsy showed ~22% blasts expressing CD13, CD33, CD34, CD117, and HLA-DR. Cytogenetics revealed 44,XY,der(1)r(1;?)(p36.?3q32;?),add(5)(p15),add(5)(q13),add(9)(q34),-17,-18[8]/46,XY[2]. Rapid molecular testing did not detect any *NPM1* or *FLT3* mutations. Results from the NGS-based gene panel would not be available for another 2 weeks. These findings were consistent with a presumptive diagnosis of AML, myelodysplasia-related post-cytotoxic therapy,[21,22] pending additional genetic results. The patient received antimicrobials to treat pneumonia. He had no other comorbidities and his ECOG performance status was 1.

What is This Patient's Prognosis?

The patient has therapy-related AML with a complex, monosomal karyotype involving monosomy 17. Twenty to forty percent of patients with therapy-related AML, 70% of patients with complex karyotype, and up to 67% with monosomy 17 and/or del(17p), will have a TP53 mutation.[14,15,56,57] Therefore, he had a high likelihood of having a *TP53* mutation.[22]

Patients with AML and a complex karyotype with or without a *TP53* mutation are considered adverse risk by ELN 2022 with a median OS of 7–10 months.[24,58,59] According to the ELN 2024 genetic risk classification for LIT, a complex karyotype is considered favourable or intermediate risk depending on the absence or presence of signalling mutations, with a median OS of ≥24 months and 12–13 months, respectively.[25,41] *TP53* mutations are considered an adverse risk with a median OS of 5–8 months.[25,41] Real-world evidence confirms the poor outcomes of patients with TP53-mutated AML with a median OS of 7.3 months, irrespective of the type of treatment administered (i.e., IC, VEN-based LIT, or single agent HMAs).[60] The only potential curative treatment for patients with *TP53*-mutated AML is an alloHCT in CR1.[61-66] However, only up to 16% of patients can receive an alloHCT.[61-64]

Multivariate analysis demonstrated improved OS in patients who were transplanted in CR1 and who had chronic graft-versus-host disease (GVHD), single-hit TP53 mutations, and non-complex karyotypes.[62-64] It remains unclear whether the intensity of the treatment (i.e., IC vs. LIT) used to achieve a CR prior to alloHCT affects outcomes in patients with *TP53*-mutated AML.[64,67-69] It is also unknown whether pre-transplant MRD positivity predicts for worse OS and increased relapse risk in this group of patients.[67]

Should the Patient Receive IC or LIT with VEN + AZA to Achieve a CR Followed by alloHCT?

IC in this clinical situation yields CR rates of 28% to 42%.[57] CPX-351 (daunorubicin and cytarabine liposome for injection) is approved for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (**Table 1**). Treatment of patients with AML with poor-risk cytogenetics with CPX-351 is associated with composite CR (i.e., CRc; CR + CRi) rates of 43.1% (CR: 34.7%).[1,2,70,71] In patients with *TP53*-mutated AML, CPX-351 yields a CRc rate of 29% with a median remission duration of 8.1 months and a median OS of 4.5 months.[1,2,70,71] Patients with ELN 2022 adverse risk AML are less likely to achieve MRD negativity than those with favourable or intermediate risk AML.[72]

Treatment with VEN + AZA yields CRc rates of 70%, a median remission duration of 18.4 months, and a median OS of 23.4 months in patients with AML with poor-risk cytogenetics without *TP53* mutations.[73] In contrast, the CRc rate was only 41%, the median remission duration 6.5 months, and the median OS 5.2 months in patients with poor risk cytogenetics and mutated *TP53*.[73] Utilization of VEN + HMA, rather than IC, may decrease treatment-related toxicities and delayed referrals to alloHCT, while increasing the proportion of patients who receive an alloHCT.[67]

Case 2 Patient Update

The patient received VEN + AZA therapy and achieved a morphological CR after 1 cycle of therapy. The BM sample sent for MFC MRD assessment was inadequate. During this period, NGS from the diagnostic BM revealed a Tier I *TP53* c.659A>G p.(Tyr220Cys) VAF 22%. Repeat BM assessment after cycle 2 of VEN + AZA revealed ongoing CR with MRD positivity by MFC at 0.17%. The patient received another 2 cycles of VEN + AZA prior to proceeding to alloHCT with a matched unrelated donor. Pre-transplant BM showed ongoing CR with routine flow analysis showing <1% CD34-positive myeloblasts. He is currently 4 months post-alloHCT, without signs of GVHD.

Conclusion

Treatment of patients with newly diagnosed AML is becoming more nuanced with the choice of therapeutic regimen dependent on patient-related factors (including age, presence of comorbidities, and fragility) and disease biology, such as cytogenetic abnormalities, gene mutations, and co-mutations, and the persistence of leukemic cells after therapy (i.e., MRD). This also highlights the need for rapid turnaround times for genetic test results to provide upfront risk stratification, guiding treatment decision-making and subsequent disease monitoring. The ongoing randomized Phase 2 studies comparing IC with VEN + AZA are expected to provide further information concerning the appropriate treatment for newly diagnosed adult patients with AML.

Off-Label Drug Use
This paper discusses the use of venetoclax and azacitidine in intensive chemotherapy-eligible patients with newly diagnosed AML.

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