

REVIEW ARTICLE

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New approaches in treatment of acute myeloid leukemia

 Ebru Koca*Baskent University, Faculty of Medicine, Department of Hematology, Ankara, Turkey*Received 28 February 2022; Accepted 14 March 2022
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**Abstract**

Historically acute myeloid leukemia (AML) treatment was limited to standard intensive induction chemotherapy with a combination of cytarabine and anthracycline for fit patients and non-intensive strategies with hypomethylating agent (HMA) or low dose cytarabine (LDAC). Allogeneic stem cell transplantation has also become an important treatment option that prolongs survival in selected patients. Over the last years with a better understanding of genomic and molecular pathogenesis of the disease, new treatment options have emerged with the contribution of translational studies. Especially less intensive frontline options have expanded. The combination of targeted therapies and standard therapies has helped to overcome treatment resistance and led to prolong survival. In this article, new approaches and especially targeted agents in the treatment of AML are discussed.

Keywords: Acute myeloid leukemia, treatment, targeted therapy, novel therapies**Introduction**

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. It is a disease of older adults with median age of 68. It is clinically and biologically heterogeneous and characterized by the clonal expansion of myeloid blasts. Acquired somatic mutations accumulated in hematopoietic stem cells and progenitor cells constitute the main pathogenesis of AML [1]. The updated 2017 European LeukemiaNet risk classification guideline, which combines cytogenetic abnormalities and genetic mutations, is widely used to determine the prognosis of AML patients [2]. Treatment of AML is separated into remission induction therapy, and postremission or consolidation and maintenance therapy for selected patients. The conventional therapy for fit patients is intensive chemotherapy with cytarabine and anthracycline, for unfit patients hypomethylating agents (HMA) or low dose cytarabine (LDAC). “3+7” regimen (3 days of daunorubicin or idarubicin and 7 days of cytarabine) was developed in the late 1970’s and has been the standard to date. However results have been dismal with 5-year expected survival 30-35% in patients under 60 years of

age and 10-15% in patients over 60 years of age [3,4]. For patients with advanced age, remission rate is significantly inferior and treatment related toxicity are higher compared to younger patients. Allogeneic stem cell transplantation (alloHCT) is a treatment option that prolongs survival in selected patients. AML is actually an umbrella diagnosis that includes many subtypes with different prognoses. In the modern era AML treatment selection is not only influenced by the patient fitness and goals but especially disease specific features like cytogenetics, mutations, pathophysiological pathways. For example, acute promyelocytic leukemia can be cured over 80% with the combination of all-trans retinoic acid and arsenic trioxide, which is a chemotherapy-free regimen [5]. The number of new drugs approved by the United States Food and Drug Administration (FDA) has increased and the treatment of AML has changed significantly in recent years (Table 1) [6]. Targeted therapies have been developed with the better understanding of the molecular landscape in AML and advancement of basic science and translational research [7]. In this article current treatment options and especially new targeted therapies will be discussed.

Clinical And Research Consequences**New Intensive Chemotherapy Options**

It has been shown that better responses can be obtained by adding nucleoside analogs (fludarabine, clofarabine, cladribine) to the standard regimen containing anthracycline and cytarabine. Adding

*Corresponding Author: Ebru Koca, Baskent University, Faculty of Medicine, Department of Hematology, Ankara, Turkey
E-mail: eburkoca@gmail.com

gemtuzumab ozogamicin (GO), a monoclonal antibody against CD33 in CD33 positive patients might also yield better results [8]. In some studies, high-dose cytarabine used as induction therapy demonstrated better results [9]. The optimum dose in high-dose cytarabine protocol for consolidation has been studied for many years. Some centers prefer 1.5 to 2 g/m² over 3 g/m² because of same efficacy with less toxicity.

FLAG-IDA is a protocol consisting of cytarabine, fludarabine and idarubicin. In one study, 8-year survival was found to be 66% in the arm that received two courses of FLAG-IDA and 2 courses of high-dose cytarabine, compared to 47% in the standard 3+7 treatment arm [10,11]. Combination of FLAG-IDA and GO in newly diagnosed AML patients under the age of 65 showed a complete response rate of 82% and 5-year survival rate of 52% [12]. Combinations of other nucleoside analogues (clofarabine, cladribine) with standard chemotherapy in induction were also studied in young patients. In a 400-patient study, the addition of cladribine to the 3+7 regimen had a complete response rate of 64% vs. 46% ($p=0.0009$), and leukemia-free survival was 44% vs. 28% ($p=0.05$) [13]. Therefore, FLAG-IDA; clofarabine/idarubicin/high-dose-cytarabine (CIA); cladribine/idarubicin/high-dose cytarabine (CLIA) might be promising alternative choices to standard therapy in first-line treatment in young patients. Studies are ongoing with new targeted agents and combination therapies.

Core Binding Factor (CBF)-AML constitutes a subset of 15% of all AMLs. It involves inv16, t(16;16) and t(8;21) chromosomal abnormalities. Historically, cure rate has been around 50% after “3+7” induction and 3-4 cycles of high-dose cytarabine consolidation. However, with the optimization of combination therapies (such as fludarabine+high-dose cytarabine) and the addition of GO, 5-year survival was increased to 75-80% [14,15]. Therefore, GO is now considered an integral part of the treatment of CBF-AML. Meanwhile, the adverse effects of FLT3, c-KIT, RAS mutations seen in CBF-AML on survival were not seen with the FLAG-IDA regimen [8].

Targeted Therapies

Venetoclax

BCL-2 a member of the BCL-2 family of anti- and proapoptotic proteins, protects the cell from apoptosis. BCL-2 expression in AML is associated with decreased sensitivity to cytotoxic chemotherapy and a higher rate of recurrence [16]. Venetoclax is a very selective BCL-2 inhibitor. It increases mitochondrial outer membrane permeability while accelerating the activation of the intrinsic apoptotic pathway. Venetoclax is very effective in chronic lymphocytic leukemia, and studies continue in some other cancer types (acute lymphoblastic leukemia, myelodysplastic syndrome, lymphoma and some myeloma subtypes) [8]. It was first approved by FDA in 2016 for treatment of chronic lymphocytic leukemia.

AML blasts and stem cells depend on BCL-2 for survival. It was seen that venetoclax was mildly effective in relapsed AML as a single agent [17,18]. Therefore, venetoclax was studied in combination with HMA and LDAC in elderly and newly diagnosed patients who were not suitable for high-dose chemotherapy. As a result of these single-arm studies, FDA approved combination use of venetoclax with HMA or LDAC [19,20]. In VIALE-A phase

3 study, newly diagnosed AML patients aged 75 years and older who could not receive intensive chemotherapy were divided into two groups as azacitidine and azacitidine/venetoclax. Survival was 14.7 months in the combination arm and 9.6 months in the azacitidine arm ($p<0.001$) [21]. Response rates were also better (66.4% vs 28.3% ($p<0.001$)). Similarly, in the VIALE-C phase 3 study, LDAC and venetoclax combination treatment showed better results than cytarabine alone. Median survival was 8.4 months in combination arm and 4.1 months in cytarabine arm ($p=0.04$); overall response rates were 48% vs. 13% ($p<0.00$), and complete response rates were 27% vs. 7% ($p<0.001$), respectively [22]. However, in a single-arm study of elderly patients (median age 72 years) with de novo AML, 10 days of decitabine induction with venetoclax on days 14-21 combined with maintenance of decitabine 5 days per month, complete response was found 67%, 4-week mortality was 0, and median survival was 18.1 months [23].

More intensive treatment combination studies with venetoclax are also ongoing. A phase Ib/IIa study conducted at MD Anderson Cancer Center, FLAG-IDA venetoclax combination (7-14 days in induction, 5-7 days in maintenance) in younger and fit newly diagnosed or relapsed/refractory AML patients was also promising. In final results, overall response rate was 84% in a total of 62 patients (27 newly diagnosed AML and 35 relapsed/resistant AML). While this rate was 89% in newly diagnosed patients, it was 66% in the relapsed/resistant group. At the end of the median 11-month follow-up, median OS was not reached [24]. Therefore, the addition of venetoclax to the FLAG-IDA protocol yielded very effective results with an acceptable safety profile. In the CAVEAT study, 51 patients with de novo or secondary newly diagnosed AML were treated with 3+5 induction and venetoclax dose cohorts. Consolidation was given 4 times (cytarabine 2 days, idarubicin 1 day) with the same venetoclax doses. Venetoclax was given for 7 days as maintenance every 28 days. Although the overall response rate was 72%, this rate was 97% in de novo AML and 43% in secondary AML [25]. Again, the addition of venetoclax to cladribine, idarubicin and cytarabine (CLIA) was found to be safe and effective in newly diagnosed AML. This combination was not found to be associated with early mortality and prolonged myelosuppression, but it was observed that the duration of MRD negativity was prolonged [26]. When venetoclax, cladribine, and low-dose cytarabine were added alternating with hypomethylating agents in elderly newly diagnosed AML patients, 94% complete response (CR/CRi) was achieved. The 4-week mortality of the well-tolerated regimen was 0%. MRD negativity was also 92% in patients with complete response in which all cell counts were recovered. In the 11-month follow-up, the median overall survival was not reached, but the 12-month overall survival was 70% [27]. In relapsed/resistant AML, when venetoclax was given with CPX-351 (300 mg on days 2-8) for 7 days, the overall response rate was 44% with a better result in venetoclax naive patients [28]. Preclinical and clinical combination studies targeting BCL-2 inhibition and other pathways (such as FLT3 inhibitors, IDH1 and 2 inhibitors, MCL-1 inhibitors, BET inhibitors, BTK inhibitors) are also ongoing.

Regimens with venetoclax have a few major limitations. Most important hematologic toxicity is neutropenia. If patient is in remission granulocyte-colony stimulating factor support provides

minimal benefit. Instead, reducing or withholding doses is advised. Resuming treatment in lower dose and reducing HMA and LDAC doses and extending intervals are recommended. However data is lacking on long term effect of these modifications on survival or relapse. Venetoclax is metabolised via CYP3A4 and other CYP3A4 inhibitors may increase venetoclax blood levels. Frequently used drugs like azoles and quinolone antibiotics may have strong interactions creating a need to reduce the dose of venetoclax dose by %50-75 [6].

IDH1/2 Inhibitors

IDH1/2 mutations are found in 5-15% of newly diagnosed AMLs [29]. Mutation in one of these genes causes an increased concentration of 2-hydroxyglutarate (2-HG) which leads to DNA and histone hypermethylation. Thus, a block in cellular differentiation followed by tumor formation occurs. Small molecules ivosidenib for mutant IDH1 AML and enasidenib for mutant IDH2 have been developed. Their safety profiles and efficacies are very similar. In a phase 1-2 study, 109 relapsed/resistant AML patients with IDH2 mutations received enasidenib 100 mg daily and the overall response rate was 40.3%; complete response was 19.3%; and median survival was 9.3 months [29]. FDA approved enasidenib in relapsed/resistant AML after this study. In a phase 1-2 study, 125 relapsed/resistant AML patients with IDH1 mutations received 500 mg/day ivosidenib and overall response was 41.6%; complete response was 21.6% and median survival was 8.8 months [30]. Based on this study, FDA approved its use in IDH1 mutant AML patients who were relapsed/resistant and couldn't receive intensive chemotherapy. Uncommon but important side effects for both drugs were prolongation of QT interval and differentiation syndrome. In a randomized phase 2 study, 101 elderly patients with newly diagnosed IDH-2 mutant AML were randomized to receive either azacitidine or azacitidine plus enasidenib (n=68). Results of the combination therapy were better (CR rate 50% vs 12%, p=0.0002). Disease-free survival was 10.8 months versus 17.2 months (HR 0.59; p=0.13), respectively. Median survival was 22.3 months versus 22 months, respectively. However, 24% of patients in the azacitidine arm received enasidenib alone as a rescue treatment [31]. In another single-arm study, 134 fit and young newly diagnosed AML patients with IDH mutation received ivosidenib (for IDH1 mutation) or enasidenib (for IDH2 mutation) in addition to 3+7 treatment. Overall response in IDH-1 mutant patients was 93% with 1-year survival of 79% and in IDH2 mutants, overall response was 73% with 1-year expected survival of 75% [32]. IDH inhibitors are oral agents that are appealing choices for older unfit patients. It must be remembered that venetoclax combinations are also very effective in IDH1/2 mutated AML [33].

FLT3 Inhibitors

FLT3 is a transmembrane tyrosine kinase receptor which promotes proliferation and survival of normal hematopoietic progenitors via different intracellular pathways. FLT3-ITD mutation is a well known poor prognostic factor. Studies with FLT-3 inhibitors have been ongoing for about 20 years. Type 1 inhibitors (midostaurin and gilteritinib) are active against both FLT3-ITD and FLT3-TKD mutations. Type 2 inhibitors (orafenib, quizartinib) are only effective against FLT3-ITD mutations. New generation agents are more effective than the old ones. Gilteritinib, a type 1 FLT3

inhibitor, showed complete response rates of 45-50% at a dose of 120 mg/day as a single agent in relapsed refractory AML. FDA approved gilteritinib based on ADMIRAL trial (n=371), which compared gilteritinib with salvage chemotherapy, showing longer survival (9.3 months vs. 5.6 months, p=0.0007) and a higher complete response (21% vs 11%, p=0.013), respectively [34]. First-line, salvage and maintenance studies are ongoing with gilteritinib, HMA, intensive chemotherapy, and venetoclax.

Quizartinib is a potent type 2 FLT3 inhibitor. The most important dose-limiting side effect is prolongation of QT interval. In randomized QUANTUM-R study, quizartinib was compared with the investigator's preferred rescue regimen in patients with relapsed refractory AML with FLT3-ITD mutation [35]. Due to very short EFS, it was not approved by FDA. However, combination studies continue. There are also studies in which FLT3 inhibitors are used as first line. In RATIFY study, 717 newly diagnosed FLT3 mutant (77% FLT3-ITD, 23% FLT3-TKD) AML patients under 60 years of age received 3+7 chemotherapy with and without midostaurin. Addition of midostaurin made a great difference in median survival (74.7 months vs. 25.6 months, p=0.009) [36]. Expected 5-year survival rate was 50% versus 42%, respectively.

Studies with new generation FLT3 inhibitors continue. In a study in which 79 newly diagnosed AML patients (56% FLT-3 mutants) were included, gilteritinib was added to 3+7 and overall response rate was 82% and 2-year survival was 72% [37]. Sorafenib was added as maintenance after alloHSCt and showed improvement in survival and disease-free survival [38]. Meanwhile, improvements were observed in studies with high-dose cytarabine, cladribine, and high-dose daunorubicin in FLT-3 mutant AML [7].

Other Important New Agents

CPX-351: CPX-351 is a nanoscale liposomal formulation of cytarabine and daunorubicin at a fixed ratio of 5:1. After promising phase 1-2 studies in secondary leukemia, a phase 3 study compared CPX-351 (n=309) with standard 3+7 (n=351) treatment. CPX-351 was associated with longer survival, better response (38% vs 26% complete response, p=0.035) and longer myelosuppression. However, more patients proceeded to allogeneic transplantation (20% vs 12%) [39]. This allowed FDA approval. Recently, CPX351 is the only drug found to be better than standart intensive chemotherapy in secondary AML.

Glasdegib: Hedgehog signaling pathway plays a critical role in embryogenesis and stem cell maintenance. Disruption in this pathway may lead to proliferation of leukemic stem cells [40]. Glasdegib is an orally available selective Smoothened receptor inhibitor in Hedgehog signaling pathway. In a phase 2 study, glasdegib was added to low-dose cytarabine and showed increased survival compared to the group that was not added. Median survival was 8.8 versus 4.9 months [41]. FDA has approved its combination with low-dose cytarabine in newly diagnosed AML patients over 75 years of age who are not eligible for high-dose chemotherapy. Other combination studies are also ongoing.

APR-246: TP53 mutant AML is associated with advanced age, treatment-related leukemia, complex cytogenetics, and poor prognosis. In combination with hypomethylating agents and venetoclax, the response rate in fit patients was 55%, but the median

survival was 6 months. APR-246 acts by inducing apoptosis. In a study involving elderly patients with MDS, AML, and CMML (n=55), a complete response of 53% was observed and median survival was 11.6 months [42].

Magrolimab (CD47 Antibody): CD47 protein is a macrophage checkpoint protein and prevents tumor cells from being destroyed by macrophages. It is overexpressed in AML cells and is associated with a poor prognosis. Magrolimab is a human monoclonal antibody that binds to CD47. Combination with azacitidine in newly diagnosed AML patients (n=34) who were not eligible for intensive treatment, response rate was 65% [43]. In 21 patients with TP53 mutation, the overall response was 71% and the complete response was 42%. The median survival was 12.9 months in patients with mutations and 18.9 months in patients without mutations.

Oral Azacitidine In Maintenance: For many years, benefit of

maintenance therapy on survival could not be demonstrated. However, FDA approved oral azacitidine as a result of the positive results in the QUAZAR AML-001 study performed with oral azacitidine (CC-486) for maintenance [44]. In this study, 472 patients over 55 years of age with adverse karyotype were given CC-486 300 mg/day for 14 days per month or placebo. The median survival was 24,7 months versus 14,8 months in favor of CC-486 (p=0.0009). In another study, 116 patients over 60 who had complete response to 2 cycles of intensive therapy, received azacitidine for 50 mg/m² for 5 days per month for 12 months as maintenance in study arm and other arm did not receive maintenance. 12-month disease-free survival was 64% in the azacitidine arm and 42% in the other arm (p=0.04) [45]. In addition, in SORMAIN study, sorafenib was given as a maintenance for 2 years after allogeneic transplantation in FLT3-ITD mutant patients. The 2-year disease-free survival was 85% in the sorafenib arm and 53% in the placebo arm (p=0.03) [38].

Table 1. Drugs recently approved by FDA for treatment of AML [Based on reference 6]

Drugs	FDA indications
Midostaurin with intensive chemotherapy	FLT3 mutant AML
CPX-351	Secondary AML, AML with myelodysplasia related changes
Glasdegib with LDAC	Unfit for intensive chemotherapy or >75 yo
Venetoclax with LDAC	New AML >75 yo or unfit for intensive chemotherapy
Venetoclax with HMA	New AML >75 yo or unfit for intensive chemotherapy
Ivosidenib	New AML >75 or unfit or relapsed refractory AML with IDH1 mutation
Enasidenib	Relapsed refractory AML with IDH2 mutation
Gemtuzumab Ozogomicin	Relapsed refractory AML with CD33+AML with intensive chemotherapy
Gilteritinib	Relapsed refractory AML with FLT3 mutation

Table 2. Current induction approaches in treatment of AML based on ESMO guidelines [7,45]

New diagnosed AML eligible for intensive therapy	CBF AML	7+3+GO*
	tAML or MRC-AML>60 years	CPX-351
	FLT3-ITD+ or FLT3-TKD+	7+3+midostaurin
	ELN favourable or intermediate risk	7+3 or
		7+3+GO*
	ELN adverse risk	7+3 or
		7+3+cladribine or 7+3+fludarabine
	Pretreated with HMA for MDS	HMA+venetoclax
	Not pretreated with HMA	LDAC or 6-mercaptopurine or melphalan or hydroxycarbamide
		HMA or LDAC+venetoclax
New diagnosed AML not eligible for intensive therapy	TP53 mutation**	clinical trial
		AZA+magrolimab
		AZA+APR-246
		HMA+venetoclax
		LDAC+venetoclax
Relapsed/refractory AML	Primary refractory, fit for intensive therapy	decitabine
		First or second alloHCT
		Cytarabine/anthracycline based re-induction
	Relapsed fit for intensive therapy	HMA or LDAC with venetoclax if available
		Or gilteritinib if FLT3-ITD/FLT3TKD mutated
		Or ivosidenib/enasidenib if IDH1/2 mutated
All others		Or melphalan
		Or best supportive care

CBF, core binding factor; GO, gemtuzumab ozogamicin; CPX-351, liposomal daunorubicin and cytarabine; ELN, European LeukemiaNet; HMA, hypomethylating agent; LDAC, low dose cytarabine; alloHCT, allogeneic hematopoietic cell transplantation; AZA, azacitidine

*GO if blasts are CD33+

**Not defined in ESMO Guideline [7]

Conclusion

The outlook for the treatment of AML has changed dramatically in recent years. We are entering a new era in the treatment of this disease with a large number of new agents. Current approaches based on ESMO guideline and examples of treatments that can be given according to AML subtypes are summarized in the Table 2. Despite all these advances, there are still unmet needs, and the results for most AML patients are not bright. We hope that eliminating minimal residual disease with immunotherapy, targeted therapy, or combination therapies may provide a final cure for some patients, with or without an allogeneic transplant. New targets can be identified and personalized treatments can be developed with the help of basic and translational research.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

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