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LEUKEMIA (A AGUAYO, SECTION EDITOR)

Treatment of Acute Myeloid Leukemia with the FLT3 Gene Mutation

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Abstract In acute myeloid leukemia (AML), mutations of the Fms-like tyrosine kinase 3 receptor (FLT3) and its overexpression are related with hyperleukocytosis, higher risk of relapse, and decrease of both disease-free survival and overall survival. It has been suggested that this phenomenon confers proliferative and survival advantages to the malignant blast cells. As a consequence, it is an attractive therapeutic target. As the best treatment strategy for mutated FLT3 AML remains to be defined, the addition of FLT3 inhibitor drugs to chemotherapy or to the bone marrow transplant approach has become a growing strategy. With encouraging results, this combination seems to be an attractive option. Relevant data regarding the current treatment trends on mutated FLT3 AML is reviewed here.

Keywords Acute myeloid leukemia treatment · FLT3 mutations · FLT3 inhibitor drugs

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Introduction

Regardless of the increased molecular comprehension of acute myeloid leukemia (AML), there have been few advances in its treatment [1]. Mutations of Fms-like tyrosine kinase 3 receptor (FLT3) and its overexpression have been identified as ominous markers in this disease and are related with hyperleukocytosis, higher risk of relapse, and decrease of both disease-free survival (DFS) and overall survival (OS) [2].

Wild-type FLT3 (FLT3-WT) is a cell membrane receptor expressed in primitive hematopoietic elements and is required for the activation of diverse cell survival pathways. Naturally, it is activated by the FLT3 ligand, which is produced by neighboring cells, progenitor cells, and by the microenvironment [3]. In 1996, Nakao et al. identified a tandem mutation in the internal juxtamembranal region of the receptor (FLT3-ITD), that drives a constitutive activation and the amplification of the FL-induced signal [3, 4]. The FLT3 gene is located on chromosome 13q12 and encodes the FLT3 tyrosine kinase receptor. Activating mutations including internal-tandem duplications (ITDs) of the juxtamembranal region (head to tail duplication of 3–400 base pairs in exons 14 or 15), tyrosine kinase domain 1, and mutations involving the D835/I836 residues and others of the tyrosine kinase domain (TKD) [47••] are identified up to 30% of adults [3] and 16.5% of children with AML [5, 6].

Driven by the success of BCR-ABL tyrosine kinase inhibition in Chronic Myeloid Leukemia (CML) [7], diverse FLT3 inhibitor drugs (FLT3ID) with spectrum against FLT3-WT, FLT3-ITD, and FLT3-TKD, have been tested [8]. Some of these drugs were initially assayed in solid malignancies of kidney, liver, pancreas, and lung, and subsequently tested in AML with aberrant FLT3 expression. As monotherapy, they all have shown a variable, limited, and brief activity. Thereafter, some of them have been integrated in combination

schemes with either conventional chemotherapy, hypomethylating drugs, protein-synthesis inhibitors, or in the context of bone marrow transplant (BMT) [9, 10••, 11, 12, 13].

Conventional Chemotherapy in AML with Mutant FLT3

The results of conventional chemotherapy regimens used in patients with mutated FLT3 AML are greatly unsatisfactory although the complete responses (CR) are comparable to the CR achieved in cases with FLT3-WT (79.6%). A difference exists with an increased relapse risk (25.6% FLT3-WT vs 75% FLT3 ITD) and decreased DFS and OS [14, 15]. Nevertheless, in the >60-year-old group, this variable has not worsened the results obtained when conventional chemotherapy alone is used [16].

In an effort for improving the conventional induction regimen results, the Eastern Cooperative Oncology Group E1900 study explored Daunorrubicin 60 vs. 90 mg/m^2 in the first induction in AML patients younger than 50 years old, and albeit the study was prematurely closed because of an excessive mortality risk, an intention-to-treat reanalysis found out that patients with FLT3-ITD were benefited by the 90 mg/m^2 dosage with better DFS and OS when compared to the lower dosage group (DFS 45 vs. 33% and OS 54 vs. 34%). This finding suggests an advantageous role for a 90 mg/m^2 dose in younger FLT3-ITD AML patients, particularly in those with a higher allele burden [17].

The clinical trials that explore the efficacy of conventional chemotherapy in mutated FLT3 AML are scarce. In this setting for a period of 15 years, the MD Anderson group studied the evolving therapeutic strategies that include the incorporation FLT3ID to conventional chemotherapy regimens. In 173 patients treated with conventional chemotherapy alone compared with 51 patients receiving a combination regimen that included FLT3ID, the CR plus CR with incomplete platelet recovery (CRp) achieved was 67 vs. 72.5% (p = 0.45). Notably, the OS showed a clear improvement throughout the time, with a rise from 9.6 months in 2000 to 17.8 months in 2014. This was probably due to the better therapeutic strategies used, including, but not limited to the FLT3ID in combined regimes and the increased usage of BMT [18•].

Tyrosine Kinase Inhibitors against FLT3

In AML, it is established that FLT3 mutations FLT3-ITD/FLT3-TKD or the overexpression of FLT3-WT confers proliferative and survival advantages to the malignant blast cells [19]. This has turned the receptor in a therapeutic target [20]. With a vision driven by the development and success of the tyrosine kinase inhibitors (TKI) used in CML, TKIs with spectrum against FLT3 have been studied [7]. Structurally, the majority of these inhibitor drugs are heterocyclic compounds that competitively inhibit the ATP-binding site in the ATP-binding pocket of the TKD. Functionally, these are multi-kinase inhibitors. As with other drugs, FLT3ID can bind to the active, inactive, and transitional state of FLT3, causing cell-cycle arrest, inhibiting proliferation and inducing apoptosis in a variety of FLT3 dependent cell lines (Fig. 1) [22•]. In AML early clinical trials, FLT3ID showed a not sustained and not robust response against FLT3 [16].

These drugs are characterized by a relatively wide spectrum of inhibition to different kinases, phenomenon that in clinical trials is associated with an incidence of several adverse effects. Although theoretically, this property would make them more able to inhibit other survival and/or proliferative pathways; in acute leukemia, this biological advantage has not been demonstrated. Actually, two generations of FLT3ID have been categorized; meanwhile, additional inhibitors are in active investigation. Each generation has different specificity, inhibition spectrum, potency, and adverse effects [8]. The first-generation FLT3ID were originally developed with other tyrosine kinases in mind, and most require a half-maximum inhibitory concentration (IC50) above 400 nM [23•]. Second generation inhibitors have been designed specifically against FLT3 with a reduced IC50 and a minor impact in other kinases.

Selected First Generation Inhibitors

Sunitinib

First FLT3ID assayed in 2005, belongs to the first generation and is a derivative of indolinone. It has unspecific activity against FLT3-ITD and FLT3-TKD, also against KIT, PDGFR, and KDR [8, 24].

Monotherapy

At doses of 50 and 75 mg for 4-week cycles, followed by a 2-week rest period in 2005, a clinical trial evaluated Sunitib as monotherapy in 16 primary or secondary relapsed/refractory AML advanced age patients, 4 of them with mutated FLT3 (ITD and TKD), with a median of 72 years old, and no candidates for induction chemotherapy. Partial responses were achieved, and best responses occurred in patients with mutated FLT3. The responses were short-sustained with a maximum of 16 weeks. The 75-mg trial was suspended for an excessive toxicity [24].

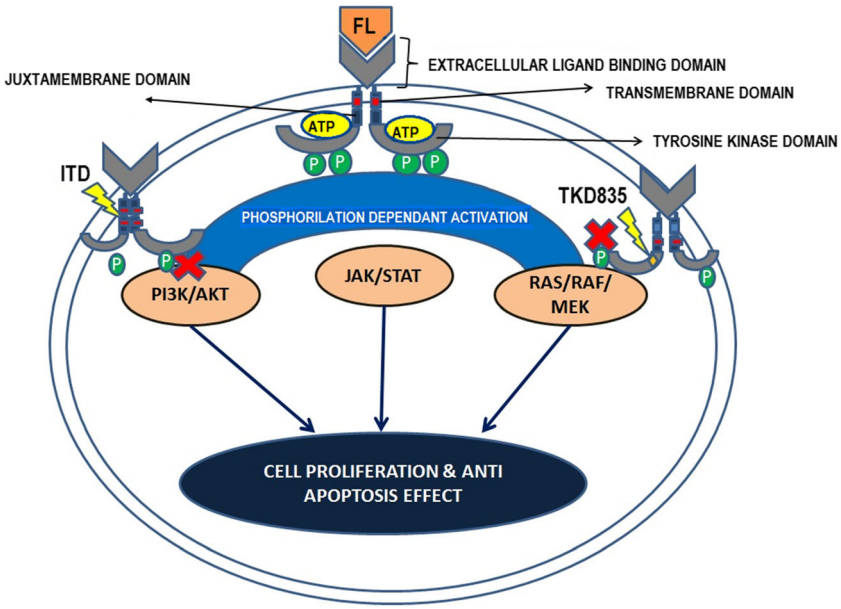

Figure 1 Schematic representation of the wild type FLT3 receptor activation by ATP and downstream stimulation of proliferative and blocking apoptosis pathways. Also, FLT3-ITD and FLT3-TKD mutant blockage by FLT3-ID and its negative effect on proliferation and anti-apoptosis pathways are shown. FL indicates FLT3 ligand; ITD internal tandem duplication; TKD 835 tyrosine kinase domain 835 mutation

Combined Therapy

In 2015, a Phase I/II Trial, Sunitinib efficacy, was studied in 22 de novo and untreated mutated FLT3 (FLT-ITD and FLT3-TKD) AML patients older than 60 years old. They received one or two induction cycles with intermediate doses of Cytarabine plus standard doses of Daunorrubicin, and then three consolidation cycles with intermediate doses of Cytarabine were added. Sunitinib 25-mg dose was administered on days 1–7 of each chemotherapy cycle and posterior to the consolidation cycles as maintenance. CR/CR incomplete (CRi) were attained in 59% (13 of 22 evaluable patients in Phase II). The principal observed toxicities were myelosuppression and associated fever [25].

Midostaurin

Compound derived from staurosporin, an alkaloid from *Streptomyces staurosporeys*. It is a multitargeted kinase, against FLT3-ITD, FLT3-TKD, and FLT3-WT as well as PKC, PDGF alpha and beta, Cdk1, Src, Fgr, Syk, c-KIT, and VEGF. Its IC50 for FLT3ITD is less than 10 nM [26].

Monotherapy

One of the first clinical trials with Midostaurin was run in 20 advanced age patients with relapsed/refractory mutated FLT3 AML or high risk myelodysplastic syndrome (MDS), who received the drug as monotherapy at 75 mg three times in a day. Two fatalities occurred because of pulmonary events of uncertain etiology. With a median of 13 weeks, the drug response was discrete and of short duration with a reduction in peripheral blood blast count in 70% of the patients. The inhibition of autophosphorylation mediated by FLT3 was documented in most of the responding patients, in whom the in vivo activity of the drug could be noted. This opened a new path for diverse clinical trials with combination therapy [27].

Combined Therapy

So far, one of the most extensive clinical trials is the international CALBG10603/RATIFY study with a cohort of 3279 newly diagnosed AML adult patients, 717 were identified with FLT3-ITD or FLT3-TKD, in whom conventional chemotherapy induction was followed by a high dose Cytarabine plus Midostaurin or Placebo, and then maintenance therapy with orally administered Midostaurin or Placebo was given.

With a median follow-up of 57 months, CR was 59% for the Midostaurin arm vs. 54% in the Placebo arm ($p = 0.18$). OS was 74.7 vs. 26 months respectively ($p = 0.007$); DFS was 8 vs. 3 months ($p = 0.004$). Notably, there was no significant difference on grades 3 or 4 therapy related adverse effects. Thereby, these results suggest that in AML patients with mutated FLT3 regardless of the allelic burden, Midostaurin can be combined with conventional chemotherapy in a secure manner and allows to achieve better results compared when it is not administered [10••].

Lestaurtinib

It is an orally bioavailable indocarbazolic alkaloid, derived from K-252a, an indocarbazole proceeding from a culture broth composed by *Nocardiopsis sp. and Nonomuraea*

longicatena [21]. In 2001, Levis et al. demonstrated its potent inhibitory properties in leukemia cell lines. In vitro experiments showed that Lestaurtinib inhibits autophosphorylation of the receptor in a dose-dependent manner, with an IC50 of 2–3 nM. Additionally, BFa3 cells with Asp835 mutation were inhibited with a similar IC50. Recent data suggests that this FTL3ID has activity against JAK2-WT and JAK2-V617F [28].

Monotherapy

Lestaurtinib 60 mg twice a day dose was evaluated in a clinical trial that included 14 relapsed/refractory high risk mutated FLT3 AML patients. Five patients had clinical evidence of biological activity and measurable clinical response, including significant reductions in peripheral blood and bone marrow blast cells. Minimal toxicity was found [29].

Combined Therapy

Derived from UK MRC AML15 and UK NCRI AML1 studies, a randomized clinical trial involving 500 mutated FLT3 AML adult patients, evaluated Lestaurtinib vs. Placebo. As a first line treatment for a 5-year period, Lestaurtinib or Placebo was added to conventional chemotherapy. Lestaurtinib dosage was 80 mg two times a day following each chemotherapy cycle for up to 28 days during 4 cycles. With a median age of 49 years, 381 patients had FLT3-ITD, 127 had FLT3-TKD, and 2 had both mutations. There was no difference in remission achieved between the two arms with CR/CRi of 92% in Lestaurtinib vs. 94% in control group. Five years DFS was 40 vs. 37% in the control group, and OS was 46 vs. 43% in the control group without significant difference. Yet, a variable analysis identified a patient subgroup with azoles concomitant administration (which has been proven to significantly raise lestaurtinib plasma levels) and Gentuzumab Ozogamizin who achieved an OS of 61% [28].

Selected Second Generation Inhibitors

Quizartinib

As a member of the second-generation FLT3ID, Quizartinib has a specific activity against FLT3, with an IC50 of 1 nM. It is 25 times more potent than other inhibitors. In mutated FLT3, it has shown an inhibition capacity against FLT3-ITD but not over FLT3-TKD. It also has an activity on KIT, PDGF alpha, PDGF beta, and CD1FR [8, 23•].

Monotherapy

The first clinical trial on refractory/relapsed AML patients was a Phase I carried out by the MD Anderson group (explored doses 12 to 450 mg daily). It included 76 adult patients with mutated FLT3 (n 17), indeterminate FLT3 status (n 22), and FLT3 negative (n 37). Patient's median age was 60 years and had three previous therapy lines. Thirty percent of them achieved a response, including 13% CR and 17% partial responses. Responses were attained in 53% of 17 mutated FLT3 patients (n 9), 41% of the 22 indeterminate FLT3 status group (n 9), and 14% of the 37 negative FLT3 patients (n 5). The median response duration was 13.3 weeks, and the median OS was 14 weeks. Drug associated adverse events included nausea 16% and QT prolongation 12%. The best-tolerated dose was 200 mg/day with toxicity limiting dose for QT prolongation [31].

Combined Therapy

A Phase I clinical trial in elderly AML patients explored Quizartinib in combination with conventional chemotherapy. Fifty-five adult patients with de novo AML were enrolled, only 4 of them had FLT3-ITD. Six cohorts with scaled doses of 60, 90, or 135 mg were categorized. Drug was administered for 7 or 14 days with a toxicity limiting dose restriction. A regimen of 40 mg/day for 14 days resulted from a de-escalation cohort due to grades 3 and 4 adverse events. Quizartinib for a 14-day period was given sequentially 2 days after each of the two courses of Cytarabine, Daunorrubicin, and Etoposide combined therapy followed by one course of Daunorrubicin/Cytarabine (2 + 5). CR was achieved in 33 of the 42 evaluable patients (79%). Reported OS is 15 months. Authors concluded that Quizartinib at 40 mg for 14 days can safely be given sequentially after chemotherapy in older patients with newly diagnosed AML [30].

Another trial tested Quizartinib integrated to a salvage chemotherapy regimen in pediatric AML patients. A dose of 60 mg/m^2/day was studied, being administered 5 days after intensive chemotherapy with 17 evaluable patients. 2CR, 1CRp, and 10 stable diseases were achieved. The near complete inhibition of autophosphorylation was evident in all patients. The drug was more efficient in FLT3-ITD than FLT3-WT [32].

Sorafenib

It is a multi-kinase inhibitor with spectrum against RAF-1, VEGFR, PDGFR, KIT and FLT3 [33]. Its clinical efficacy in AML has been explored in diverse scenarios: as monotherapy, in combination with chemotherapy during induction, consolidation and as maintenance in the post-BMT setting [16].

Monotherapy

Sorafenib was studied for the first time in 16 refractory/relapsed AML patients (7 FLT3-WT, 6 FLT3-ITD, 1 FLT3 TKD/ITD and 2 FLT3-TKD) treated in a Phase I trial. Patients were randomly assigned to receive Sorafenib in 21-day cycles of 5 days per week (n = 7 patients; arm A) or of 14 days (n = 9 patients; arm B). In both arms, the starting dose level was 200 mg twice daily. Subsequent dose levels were 600, 800 and 1200 mg daily in cohorts of three subjects at each dose level. No limiting toxicity dose was seen. Efficacy was only limited to a transitory blast reduction both in peripheral blood and bone marrow in all FLT3-ITD patients [34].

Combined Therapy

A Sorafenib Phase I/II Clinical Trial in 51 untreated, younger than 65 years AML patients, evaluated the feasibility of administering 400 mg of the drug twice a day on days 1 to 7 in combination with a continuous infusion of intermediate dose Cytarabine for 3 to 4 days plus Idarrubicin at conventional dosage for 3 days as induction chemotherapy. CR was found in 75%, nevertheless when the group was divided regarding the mutational status of FLT3, 14 of the 15 patients with FLT3-ITD achieved a CR of 94% (the 15th patient achieved a CRp), whereas the FLT3-WT patients obtained a 66% of CR. With a median follow-up of 54 weeks, the survival probability in 1 year was estimated in 74% [14].

FLT3ID (Midostaurin) Plus Hypomethylating Agents

The combination of Midostaurin with hypomethylating agents has also been explored. In a clinical trial that included a preclinical phase, AML cellular cultures were exposed to Decitabine and Midostaurin. The combination proved to be effective in vitro on cell lines that expressed the FLT3-ITD mutation. This strategy was translated into a clinical phase to a group of 16 newly diagnosed elderly or relapsed/refractory adult patients with AML, from which only 13% had FLT3-ITD. Nevertheless, the concomitant administration of drugs resulted in unacceptable pulmonary and cardiac toxicities; consequently, it was found that the best sequential administration was Decitabine followed by Midostaurin. In an intention-to-treat analysis, 75% of patients achieved a stable disease as a minimum and 25% achieved CR. These results require additional studies to evaluate their security in advanced age patients [35].

The MD Anderson group evaluated Midostaurin in combination with Azacitidine in 54 AML and high-risk MDS patients. They established two cohorts of patients with Midostaurin doses of 25 and 50 mg in combination with Azacitidine at a fixed dose of 75 mg/m^2. Overall response at a median of 12 weeks was 26%. Responses occurred in 33%. Patients with FLT3 mutations but not previously transplanted or exposed to other FLT3 inhibitors achieved the greatest benefit. Toxicity was notorious because G3–4 non-hematological toxicity was reported in 38 (70%) patients, most frequently infections (56%), ejection fraction reduction (11%), and diarrhea or nausea/vomiting (9% each) [13].

Resistance to FLT3ID

Diverse mechanisms involved in the acquired resistance to FLT3ID have been described. Notoriously, punctual mutations in the binding loop and in the activation domain, amplification of the mutated receptor, co-expression of FLT3-WT and utilization of alternative pathways to cellular survival have been reported [36•, 37, 38, 39, 40]. The MD Anderson recently found that 22% of the patients previously exposed to FLT3ID, developed punctual mutation of the TKD [48]. In this setting, Crenolanib has been identified as a potent FLT3ID able to overcome resistance induced by punctual mutations in D835 of the mutated FLT3. Besides, it has a narrow spectrum minimizing the effect on erythropoiesis; these data could position Crenolanib as a potential effective and less myelotoxic drug [41•].

BMT in Mutated FLT3 AML

In FLT3 mutated AML patients, BMT role is not totally elucidated, although several publications support its use [42, 43, 44]; others have not shown an improved outcome [45].

Brunet et al. evaluated the repercussion of FLT3-ITD mutation and a "normal" karyotype in AML patients who underwent allogeneic BMT in first CR. They studied 206 patients; 120 (58%) presented FLT3-ITD; and among these, two had a primary graft failure. When compared to the negative mutated FLT3 group, no difference in the rate of acute or chronic graft vs. host disease was noted. At 2 years, a superior relapse accumulated incidence (30 vs. 16% p = 0.006) in the group of FLT3-ITD patients was observed. Other factors that favored a higher trend to relapse were patients older than 42 years, more than one chemotherapy course before achieving CR, shorter interval between CR and BMT, and female gender. At 2 years, DFS was lower in FLT3-ITD patients (58 vs. 71% p = 0.04) [46].

In this scenario, the integration of Sorafenib 400 mg twice a day as a maintenance therapy following allogeneic BMT was proved on 22 patients in first or second CR. The drug was started between 45 and 125 days after BMT. One year follow-up DFS was 85%, and OS was 95% with an OS of 100% of patients in first CR, with just one case of relapse [11]. When compared with trials limited to BMT alone [46], the results seem encouraging.

Following BMT, FLT3-ITD AML relapses carry a poor prognosis. Sorafenib has proven to be useful also in this

Table 1 Clinical experience on different trials using FLT3ID associated with chemotherapy or BMT in AML patients

Authors	Year	Patients (*n*)	Treatment	DFS	OS	Reference	Notes
Stone et al.	2015	*n* 717 De Novo AML (FLT3-ITD high and low allelic burden and FLT3-TKD) adult patients	Chemotherapy plus midostaurin vs. Chemotherapy plus placebo	Chemo + midostaurin 8 months Chemo + placebo 3 months	Chemo + midostaurin 74 months Chemo + placebo 26 months	[10••]	Improved OS and DFS in the midostaurin plus chemo group. 57% had a BMT.
Farhad Ravandi et al.	2010	*n* 51 AML adult patients younger than age 65 years FLT3-ITD/TKD (15) FLT3-WT (36)	Chemotherapy plus sorafenib	Not reported	Probability of survival at 1 year 74%	[14]	CR 94% in FLT3-ITD group versus CR 66% in FLT3-WT group
Brunet et al.	2012	*n* 206 AML CR1 patients, FLT3-ITD (120)	Allo-SCT at first complete remission, no FLT3ID was added	2 years: FLT3-ITD 58% FLT3-WT 71%	Not reported	[46]	FLT3-ITD patients have worse prognosis and shorter DFS than FLT3-WT patients.
Yi-Bin Chen et al.	2014	*n* 22 AML FLT3-ITD patients underwent first allogeneic BMT	Sorafenib 400mg bid between days +45 and +120 as maintenance after BMT and continued for twelve 28-day cycles.	1 year: 85% after BMT	1 year: 95% after BMT	[11]	Sorafenib is safe after BMT for FLT3-ITD AML and deserves further investigation for the prevention of relapse.
De Freitas et al.	2015	*n* 13 adult patients AMLRelapsed post Allo-BMT LMA FLT3-ITD (13)	Hypomethylating drugs/donor T cell infusion plus sorafenib or as monotherapy	Not reported	At day 100 from relapse: 65% OS (1 year) estimated at 22%	[47••]	Complete hematological Response 92%, Complete Bone Marrow Response: 38%. Therapeutic activity as salvage after BMT relapse

scenario. *De Freitas* et al. carried out a retrospective trial of Sorafenib in 13 adult patients. Sorafenib was used as monotherapy or in association with hypomethylating agents or T cell donator infusion. Hematological response was documented in 12 of the 13 patients (92%), with 5 (38%) achieving a CR in BM. Manageable adverse effects were presented, being the most common severe cytopenias and hand-foot syndrome. The OS at day 100 from relapse was 65% and at 1 year 22%. These findings suggest that Sorafenib could represent a future therapeutic option for patients with relapse after BMT, for bridging them to an additional transplant [47••].

Conclusions

When AML is treated with conventional chemotherapy, mutated FLT3 confers a poor prognosis. Its identification has driven to the development of a family of drugs capable of inhibiting its expression. Used as monotherapy, these drugs have limited and brief anti-leukemic activity. Their best contribution has been proved in combination with sequential chemotherapy or as maintenance after BMT (Table 1); in this setting, the most promising inhibitors are Midostaurin and Sorafenib.

As a predictable phenomenon, emergence of resistance to FLT3ID has already been identified. Other FLT3ID as Crenolanib are capable to overcome this condition and are being actively explored.

Until now, the best therapeutic strategy to treat mutated FLT3 AML remains to be defined. Nevertheless, available data indicates that in young patients and in the post-BMT setting, integrating FLT3ID to treatment strategies is beneficial, but further research is required.

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Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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