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REVIEW

Safety of FLT3 inhibitors in patients with acute myeloid leukemia

Claudio Cerchione [a,*], Andrés Peleteiro Raíndo[b,c,*], Adrián Mosquera Orgueira[b,c], Alicia Mosquera Torre[b,c], Laura Bao Pérez[b,c], Giovanni Marconi[a], Alessandro Isidori[d], Manuel Mateo Pérez Encinas [b,c,e,§] and Giovanni Martinelli[a,§]

[a]Hematology Unit, IRCCS Istituto Scientifico Romagnolo per Lo Studio Dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [b]Health Research Institute of Santiago De Compostela (Idis), Santiago De Compostela, Spain;; [c]Division of Hematology, Complejo Hospitalario Universitario De Santiago (Chus), Santiago De Compostela, Spain; [d]Hematology and Stem Cell Transplant Center, Aormn Hospital, Pesaro, Italy; [e]University of Santiago De Compostela, Santiago De Compostela, Spain

ABSTRACT

Introduction: Acute myeloblastic leukemia (AML) is the most frequent type of acute leukemia in adults with an incidence of 4.2 cases per 100,000 inhabitants and poor 5-year survival. Patients with mutations in the FMS-like tyrosine kinase 3 (*FLT3)* gene have poor survival and higher relapse rates compared with wild-type cases.

Areas covered: Several FLT3 inhibitors have been proved in *FLT3*^{mut} AML patients, with differences in their pharmacokinetics, kinase inhibitory and adverse events profiles. First-generation multi-kinase inhibitors (midostaurin, sorafenib, lestaurtinib) target multiple proteins, whereassecond-generation inhibitors (crenolanib, quizartinib, gilteritinib) are more specific and potent inhibitors of FLT3, so they are associated with less off-target toxic effects. All of these drugs have primary and acquired mechanisms of resistance, and therefore their combinations with other drugs (checkpoint inhibitors, hypomethylating agents, standard chemotherapy) and its application in different clinical settings are under study.

Expert opinion: The recent clinical development of various FLT3 inhibitors for the treatment of *FLT3*^{mut} AML is an effective therapeutic strategy. However, there are unique toxicities and drug–drug interactions that need to be resolved. It is necessary to understand the mechanisms of toxicity in order to recognize and manage them adequately.

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1. Introduction

The identification of recurrently mutated genes and cytogenetic anomalies in acute myeloid leukemia (AML) has proved of high prognostic and therapeutic significance in patients with this disease [1]. Among these, mutations in the FMS-like tyrosine kinase 3 *(FLT3*) gene are present in 30% of adults with newly diagnosed AML, making it the most frequently mutated gene in this type of leukemia. These mutations lead to constitutive activation of the protein product, and are divided in two broad types: *FLT3* internal tandem duplication mutation (ITD subtype; 25% of AML newly diagnosed cases) and point mutations in the tyrosine kinase domain (TKD subtype; 7–10% of patients) [21]. FLT3-ITD mutations are associated with a poor prognosis, particularly when they are accompanied by a high mutant to wild-type allelic ratio [3], whereas the prognosis of *FLT3* TKD mutations still remains uncertain. In addition, there are other factors that have an impact on the prognosis of newly diagnosed *FLT3*-ITD mutated AML patients, like ITD length, mutation insertion site, the presence of nucleophosmin 1 (*NPM1*) gene mutations and complex karyotype [4].

Due to the frequency of this driver mutation, multiple targeted agents against the FLT3 mutant protein have been developed. Recently, the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) have approved the multikinase tyrosine kinase inhibitor (TKI) midostaurin in combination with standard cytarabine and daunorubicin induction plus cytarabine consolidation in adults with newly diagnosed *FLT3*-mutated AML, making it the first AML drug to receive regulatory approval in the US since 2000. Following midostaurin, gilteritinib (a second-generation FLT3 inhibitor) was approved for use as a single agent in adults with relapsed or refractory *FLT3*^{mut} AML. Currently, there are several other *FLT3* inhibitors in different clinical trials in advanced development, and the therapeutic approach to this subtype of AML will probably change in the near future.

FLT3 inhibitors' active mechanism depends mostly on competitively inhibiting ATP-binding sites in the FLT3 receptor,

CONTACT Claudio Cerchione claudio.cerchione@irst.emr.it Hematology Unit, IRCCS Istituto Scientifico Romagnolo per Lo Studio Dei Tumori (IRST) 'Dino Amadori' Via P. Maroncelli 40, Meldola (FC), 47014, Italy; Adrián Mosquera Orgueira adrian.mosquera@live.com Division of Hematology, Complejo Hospitalario Universitario De Santiago (Chus), Avenida Da Choupana S/n, Santiago De Compostela, 15706, Spain
*Equally contributed as first coauthors.
§Equally contributed as last coauthors.

Article highlights

- The recent clinical development of various FLT3 inhibitors for the treatment of *FLT3*^{mut} AML has proved to be an effective therapeutic strategy in different clinical settings.
- FLT3 inhibitors have particular toxicities that require specific management.
- Antifungal prophylaxis deserves special attention in patients treated with midostaurin and other *FLT3* inhibitors due to their metabolic interactions with azole drugs (such as posaconazole, the standard of care antifungal agent used as prophylaxis in AML patients).
- More studies need to be carried out in order to understand the exact role of the FLT3 inhibitors in the different clinical settings of AML, as well as their possible association with other new drugs.

leading to cell cycle arrest and differentiation [5]. In addition, these agents vary in their ability to target non-FLT3 signaling pathways, which influences both their tolerability and efficacy. First-generation FLT3 inhibitors (e.g. sorafenib, lestaurtinib, and midostaurin) have less specificity for FLT3 since these are molecules that were not specifically designed to target this protein, and consequently they have additional activity against other targets such as platelet-derived growth factor receptor (PDGFR), c-Kit and vascular endothelial growth factor receptor (VEGFR) [6]. Such a lack of specificity may explain their transient antileukemic activity and their variable tolerability due to the adverse effects derived from the inhibition of multiple kinases [4]. This class of drugs have poor results in monotherapy, due to limited efficacy and/or tolerability [7,8]. In contrast, second-generation FLT3 inhibitors (e.g. crenolanib, quizartinib and gilteritinib) were designed to selectively and potently inhibit the FLT3 receptor, and these drugs presumably have an improved tolerability profile at the concentrations necessary to fully inhibit FLT3 *in vivo*. Therefore, it is essential to understand the different safety profiles of these new agents in order to carry out a more individualized treatment adapted to the needs of each patient [9].

Another classification of *FLT3* inhibitors considers the way that they interact with the *FLT3* receptor. All *FLT3* inhibitors interact with the ATP-binding site of the tyrosine kinase domain, competitively inhibiting ATP binding and thus preventing receptor autophosphorylation and activation of signaling cascades. Based on these criteria, they are divided into type I inhibitors (such as midostaurin, crenolanib, gilteritinib or lestaurtinib) and type II inhibitors (such as sorafenib, quizartinib, ponatinib) [8]. Type I inhibitors bind to the receptor in both its active and inactive conformation, whereas type II inhibitors interact with a hydrophobic region immediately adjacent to the ATP binding site that is only accessible when the receptor is in the inactive conformation. Since TKD mutations (mainly D835) favor an active conformation, type I inhibitors are active against *FLT3* in the presence of ITD or TKD mutations, whereas type II drugs inhibit *FLT3* with ITD, but not with TKD mutations; although in some cases, TKDD835 mutations may retain sensitivity (Figure 1).

In this review, we summarized currently available toxicity data of the FLT3 inhibitors that are already approved or in

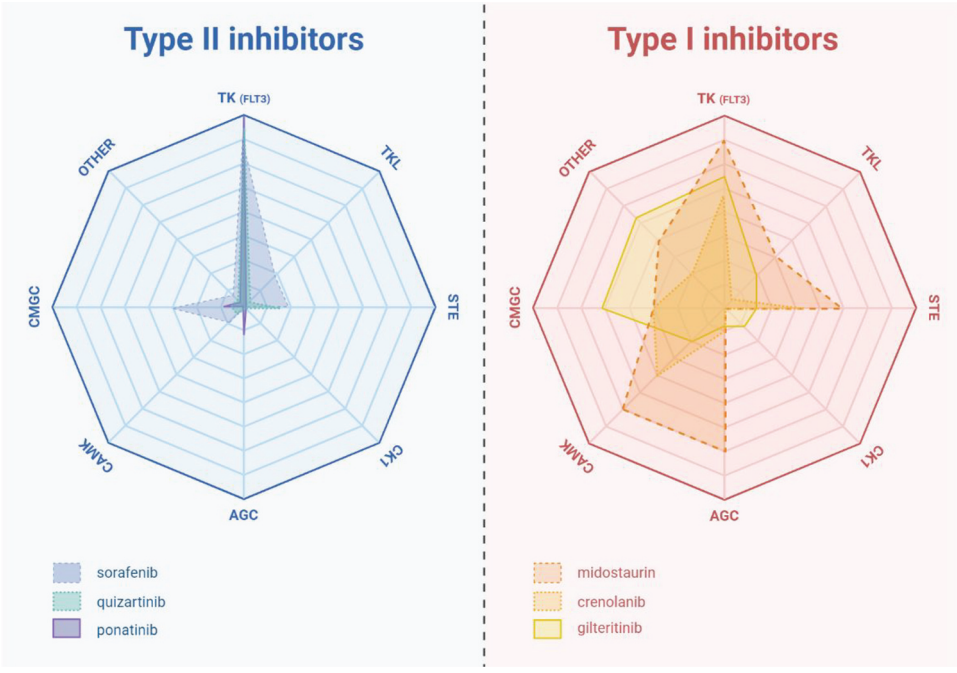

Figure 1. Specificity of inhibition of different classes of protein with kinase activity by type II and type I inhibitors. The octagon plots the TK's classes. In each TK class, for every TKI, we drew a peak from the center; the peak represents the number of TKs in the class that are inhibited by a specific TKI. The figures composed of joining the peaks are representative of the spectrum of inhibition of each TKI. Larger figures mean wider TK inhibition; TK: tyrosine-kinase family, include FLT3; TKL tyrosine-kinase like family; STE: Serine/Threonine protein kinase family; casein kinase 1 family; AGC: protein kinase A, G, and C family; CAMK: Ca2+/calmodulin-dependent protein kinase family; CMGC: CDKs, GSKs, MAP kinases, and CDK-like kinases family. Reproduced with permission from *Marconi G, et al. The safety profile of FLT3 inhibitors in the treatment of newly diagnosed or relapse/refractory acute myeloid leukemia. Expert opinion on drug safety. April 21. 10.1080/14740338.2021.1913120. [99].*

advanced development for AML treatment. We also discuss the optimal management strategies of these toxicities, and finally summarize future clinical developments in order to overcome the adverse events and interactions of these targeted therapies.

2. Midostaurin

2.1. Pharmacokinetics and pharmacodynamics

Midostaurin is rapidly absorbed after oral administration (1–3 hours), although its absolute bioavailability is unknown. Its administration is recommended together with food. It circulates mostly bound (98%) to plasma proteins. Both midostaurin and its metabolites diffuse mainly in plasma, not in red blood cells. It is metabolized by CYP3A4, giving rise to two active metabolites, CGP62221 and CGP52421. For this reason, concomitant use of midostaurin with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, enzalutamide, St. John's wort [*Hypericum perforatum*]) is contraindicated. The coadministration of 600 mg daily rifampicin at steady state (a potent inducer of CYP3A4) with midostaurin (50 mg/daily) decreased midostaurin maximum concentration (C-max) by 73% and area under the curve from 0 to infinity (AUCinf) by 96% in healthy subjects [10]. On the other hand, strong CYP3A4 inhibitors can increase the blood level of midostaurin. In a clinical trial of 36 healthy subjects, when ketoconazole (a strong CYP3A4 inhibitor) was administered at steady state with a single 50 mg dose of midostaurin, a significant increase in midostaurin concentration was observed (C-max and AUCinf rised 1.8 and 10 times, respectively). Additionally, a 3.5-fold increase in AUCinf of CGP62221 was detected, whereas the C-max of both active metabolites, CGP62221 and CGP52421, was halved [10]. Administration with strong CYP3A4 inhibitors should be avoided, and extreme caution should be taken in the case of unavoidable co-administration.

Midostaurin is an orally administered methylbenzamide, with capacity to inhibit various receptor tyrosine kinases, such as FLT3 and KIT. It inhibits FLT3 receptor signal transduction and induces cell cycle arrest and apoptosis in leukemic cells expressing mutated FLT3-ITD or TKD receptors, or overexpressing wild-type FLT3 receptors. Midostaurin also inhibits other receptor tyrosine kinases, such as PDGFR or VEGFR2, and the serine/threonine kinases of the protein kinase C (PKC) family [10] (Table 1).

2.2. Efficacy and toxicity

Midostaurin has been approved by the EMA and the FDA in combination with standard cytarabine and daunorubicin induction plus cytarabine consolidation in adults with newly diagnosed *FLT3*^{mut} AML. This approval was motivated by the compelling results of the RATIFY trial [11], which was a randomized multicenter phase 3 trial in which patients were randomly assigned to receive standard chemotherapy plus either midostaurin or placebo. Patients who were in remission after consolidation therapy started a maintenance phase in which they could receive either midostaurin or placebo. Induction treatment consisted of standard 3 + 7 chemotherapy (daunorubicin 60 mg/m2 on days 1–3, plus cytarabine 200 mg/m2 on days 1–7), plus either placebo or oral midostaurin 50 mg bid on days 8 to 21. A second chemotherapy course with placebo or midostaurin was administered in case of clinically significant residual disease. Patients who achieved a complete remission after induction received 4 consolidation cycles of high-dose cytarabine (3,000 mg/m2 administered over a period of 3 hours every 12 hours on days 1, 3 and 5) plus placebo or oral midostaurin 50 mg bid on days 8 through 21. Patients who remained in complete remission were assigned to maintenance therapy with oral midostaurin 50 mg bid for twelve 28-day cycles or placebo. Allogeneic stem cell transplantation was performed at the discretion of the investigator. Although midostaurin dose was planned to be 100 mg b.i.d. continuously following chemotherapy, both the dose and the duration of treatment had to be reduced to 50 mg bid due to gastrointestinal toxicity. The primary endpoint of the trial was overall survival (OS), which was defined as the time from randomization to death from any cause. Event-free survival was a secondary objective, defined as time from randomization to relapse, death from any cause or failure to achieve protocol-specified complete remission. Patients in the midostaurin group had a significant improvement in OS (4-year OS rate: 51.4% versus 44.3%; median OS: 74.7 months versus 25.6 months; p = 0.009), an effect that was independent of the type of FLT3 mutation or the ITD allelic burden (i.e. <0.5 or □0.5).

The most common adverse reactions were nausea (83.4%), febrile neutropenia (83.4%), mucositis (61.6%), vomiting

Table 1. Characteristics of FLT3 inhibitors in clinical development.

FLT3 INHIBITOR	TYPE OF INHIBITOR	NON-FLT3 TARGETS	FLT3-TKD MUTATION ACTIVITY	DOSE	METABOLIC PATHWAY	MAJOR TOXICITIES
Midostaurin	First generation. Type I	c-KIT, PKC, PDGFR, VEGFR	Yes	50 mg b.i.d.	Liver: CYP3A4	Gastrointestinal, myelosuppression
Sorafenib	First generation.Type II	c-KIT, PDGFR, RET, VEGFR	No	400 mg b.i.d.	Liver: CYP3A4 as well as UGT1A9	Rash, hemorrhage, myelosuppression
Gilteritinib	Second generation. Type I	AXL, EML4-ALK	Yes	120 mg daily	Liver: CYP3A4	Elevated transaminases, diarrhea
Quizartinib	Second generation. Type II	c-KIT, PDGFR, RET	No	30–60 mg q. o.d	Liver: CYP3A4	QTc prolongation, myelosuppression
Crenolanib	Second generation. Type I	PDGFR, c-KIT	Yes	100 mg t.i.d.	Cytochrome P450	Gastrointestinal

Legend: PDGFR, platelet-derived growth factor receptor; tid, three times daily; TKD, tyrosine kinase domain; VEGFR, vascular endothelial growth factor receptor.

(60.7%), headache (45.9%), petechiae (35.8%) and fever (34.5%). Other less frequent adverse reactions were musculoskeletal pain, epistaxis, catheter-related infection, hyperglycemia, and upper respiratory tract infections, but not too many significant differences were observed between the two treatment groups in the rates of adverse events of grade 3, 4, or 5. In comparison with the placebo group, the midostaurin group had higher rates of grade 3, 4 or 5 anemia (92.7% vs. 87.8%, P = 0.03) and also higher rates of grade 3, 4, or 5 rash (14.1% vs. 7.6%, P = 0.008). On the other hand, the rate of nausea was higher with placebo (9.6 vs. 5.6%, P = 0.05). There were no statistically significant differences in neither the median time to recovery of absolute neutrophil count (>500 neutrophils per microliter), which was 26 days in both groups (interquartile range, 22 to 31 in placebo group and 24 to 30 in the midostaurin group) nor in the median time to recovery of the platelet count (to >100,000 per microliter), which was 21 days in both groups (interquartile range, 19 to 23 in the midostaurin group and 19 to 24 in the placebo group). Discontinuation due to any adverse reaction occurred in 9% of patients in the midostaurin group versus 6% in the placebo group. Excluding deaths due to disease progression, there were no fatal adverse reactions in the study. Overall, the most common cause of non-treatment-related death in the midostaurin plus chemotherapy arm was sepsis (2%), with the same incidence rate as in the control arm [11].

During maintenance therapy, the most common adverse reactions in the midostaurin *versus* placebo arm were: nausea (46.4% versus 17.9%), hyperglycemia (20.2% vs. 12.5%), vomiting, (19% vs. 5.4%) and QT interval prolongation (11.9% vs. 5.4%) [10]. An effect of maintenance therapy on survival has not been demonstrated in the RATIFY trial, so this indication is under debate. Gastrointestinal, infections, blood count changes, pain, allergies, and dermatological and renal adverse events are more commonly observed in patients starting maintenance therapy after allogeneic SCT, whereas a trend toward more cardiac arrhythmias was observed after HiDAC consolidation [12].

2.3. Off-target toxicity

There are no well characterized molecular mechanisms responsible for midostaurin's off-target toxicity, although this drug is among the least specific FLT3 inhibitors available. Cardiac effects described in patients treated with midostaurin, such as cardiac failure (1–6%) or ischemia (4%), have been hypothesized to be a possible consequence of VEGFR2 inhibition [13]. Furthermore, midostaurin-associated myelosuppression is probably mediated by inhibitory activity against c-KIT, a side effect which is common to all inhibitors of this protein [14].

2.4. Midostaruin and antifungal prophylaxis

The drug interaction profile of midostaurin is particularly important in the case of antifungal prophylaxis in AML patients, since posaconazole (a strong CYP3A4 inhibitor) is the standard of care antifungal agent used for prophylaxis during induction treatment [15]. Several approaches have been proposed to best prevent potential drug–drug interactions (DDI) in concomitant administration of midostaurin and antifungals [16]. The use of posaconazole concomitant to 50 mg b.i.d. of midostaurin has been recommended in several publications assuming no significant increased risk of DDI [17,18]. These dosages, which should provide the necessary antileukemic activity, have been investigated under trial conditions [10,19]. However, this approach may trigger midostaurin-related severe adverse events (AEs) and expose patients to unpredictable risks. For this reason, other authors have considered that the risk of DDI may be clinically important. Thus, a robust clinical trial investigating this issue is still awaited.

Another approach consists of decreasing midostaurin dose by 50% (i.e. 25 mg b.i.d) during induction treatment. This strategy has been proposed and implemented in some centers [12], and it seems a reasonable option for reducing the risk of dose-related midostaurin toxicity while enabling the use of posaconazole as a prophylactic agent. This option could be a good choice in elderly patients undergoing intensive induction. In fact, *Schlenk et al* presented the results of a phase II study comparing the efficacy and safety of the addition of midostaurin to standard AML treatment, and compared outcomes among older patients (age 61–70 years) with historical controls. Antifungals were allowed as comedication. After an amendment of the protocol, a midostaurin dose reduction to 25 mg bid was allowed in case of coadministration with strong CYP3A4 inhibitors. Mortality among older patients was substantially lower among those patients who were treated after protocol amendment (2.4% vs 15.7%), a finding which could be related to reduced midostaurin toxicity [12]. However, this strategy seems questionable without availability of midostaurin blood levels or FLT3 activity determination, as the underdosing of midostaurin may lead to decreased antileukemic activity. Therefore, this strategy should be currently considered off-label and additional studies are warranted in this scenario [12].

A third option would be to change the class of antifungal prophylaxis, for example, by using echinocandins (EC). Micafungin is broadly used in patients who are intolerant to posaconazole, and in patients undergoing allogeneic SCT for *Candida*-oriented prophylaxis [20,21]. Micafungin prophylaxis has demonstrated similar results compared to fluconazole among similar patient populations in efficacy studies [22,23]. It has even been suggested as an alternative prophylactic agent in AML [22,24]. Notwithstanding, this recommendation is provided from studies with limited statistical power. Similarly, caspofungin has been used in prophylaxis in AML patients, with similar results [25,26]. Nevertheless, EC are inactive against some *Fusarium* and *Mucorales* species, which are isolated with increasing frequency among patients with hematological malignancies [27–30]. As another drawback, ECs are only available in intravenous formulations.

Another appealing option for primary antifungal prophylaxis is the use of isavuconazole, which is a moderate CYP3A4 inhibitor. In AML and MDS patients, this drug has proved its safety and effectiveness at 200 mg or 400 mg

qod [31,32]. Isavuconazole is an extended spectrum triazole agent approved for treatment of invasive mucormycosis and aspergillosis [33,34]. However, data about its efficacy in primary prophylaxis are contradictory. Some studies have reported higher rates of breakthrough invasive fungal infections (bIFI) (such as invasive pulmonary aspergillosis and Candida infections) compared to voriconazole or posaconazole [35–37], especially in scenarios of profound neutropenia, whereas other studies didn't reveal any differences between agents in bIFI rates [38]. However, the interpretation of such studies is hindered by differences in defining bIFIs, heterogeneity among patient populations receiving prophylaxis and study designs. These findings suggest that additional studies are needed to determine the role of isavuconazole as primary prophylaxis in patients with AML. On the contrary, voriconazole is not superior to posaconazole as a prophylactic agent and its effects on the CYP3A4 are similar, so this drug does not appear to be a good option in this setting [39].

Finally, another approach foresees the implementation of therapeutic drug monitoring (TDM) for both posaconazole and midostaurin in patients receiving these drugs concomitantly, and adapt dosification according to drug levels [16]. However, the standardization of TDM is still a challenge among patients treated with midostaurin. In the near future, the availability of standardized TDM methods could allow individualized dosing of anti-infective and oncological drugs. This last approach would contribute to a personalized management of AML patients receiving midostaurin and posaconazole concomitantly and may provide the most efficient and safest way to avoid adverse events.

2.5. Dose adjustments

Midostaurin has to be interrupted if a QTc interval > 500 ms is detected during therapy. In case that the QTc interval is between 470 and 500 ms, midostaurin has to be reduced to 50 mg qod. Midostaurin can be restarted to the original dose if the QTc interval is ≤470 ms at the starting point of the next cycle [11]. For this reason, an electrocardiogram (ECG) is necessary before starting treatment with midostaurin and periodic monitoring of electrolytes (potassium, magnesium, calcium) and ECGs should be performed during treatment. No dosage adjustment is necessary in patients with mild or moderate renal impairment. Among patients with severe renal impairment, clinical experience is limited and there is no data in patients with end-stage renal disease. In a similar way, no dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B), but no experience exists in patients with severe hepatic impairment [11] (Table 2).

2.6. Use in older patients

As the RATIFY trial did not included patients >59 years old [11], midostaurin safety data in elderly patients arises from a phase 2 trial that evaluated the safety of adding midostaurin to intensive chemotherapy in older (up to 70 years old) FLT3-ITD positive AML patients. This trial contemplated undergoing an allogeneic SCT plus maintenance for 12 months or allogeneic SCT alone. The dose of cytarabine was 1 g/m2 for those patients over 65 years old. Patients aged 60 years and over (n = 86) presented more cardiac toxicity (especially arrhythmias) and an increased rate of pneumonia, without significant differences in the rest of toxicities. Therefore, a greater control of heart rhythm in patients over 60 years is recommended. Post-allogeneic SCT maintenance was also evaluated in this trial, revealing an increased rate of gastrointestinal toxicity, cytopenias and rash compared to post-cytarabine consolidation therapy. Notably, midostaurin efficacy was similar to that of younger patients [17]. As midostaurin is not approved as post-allogeneic SCT maintenance, the technical data sheet indicates that it must be suspended 48 hours before the start of conditioning. Recently, results from a phase 3b trial have been presented that evidence greater toxicity in older patients, especially infections, leukopenia, QT interval prolongation and pulmonary toxicity, but without a reduction on the rate of complete remissions [40].

3. Sorafenib

The efficacy and safety of sorafenib in AML has been studied in various clinical trials, without ever having obtained approval for this pathology in any of its settings. The largest study to date is the SORMAIN trial, which was a randomized, double-blind, placebo-controlled and multicenter trial designed to study the effect of sorafenib maintenance after allogeneic SCT in *FLT3*^{mut} AML patients in complete remission [41]. Despite not being approved for the treatment of AML, sorafenib has been one of the first and most widely used FLT3 inhibitors due to its availability for the treatment of other pathologies such as renal cell, hepatocellular or thyroid carcinoma.

3.1. Pharmacokinetics and pharmacodynamics

Sorafenib is an orally administered multikinase inhibitor in the form of the tosylate salt of sorafenib. The antiproliferative activity of sorafenib varies depending on the type and mechanism of tumor proliferation. It was originally developed as an inhibitor that targets the Raf kinase and MAPK signaling pathway, but it was found to also have potent inhibitory activity against FLT3, VEGFR, PDGFR, c-Kit, and RET [42] (Table 1). After oral administration, it reaches plasma peaks in approximately 3 hours. Steady-state plasma concentrations are reached in 7 days and its elimination half-life is approximately 25–48 hours. The absorption of sorafenib is reduced by 30% after a high-fat meal, compared to administration on an empty stomach. Binding of sorafenib to human plasma proteins *in vitro* is 99.5%. Sorafenib is primarily metabolized in the liver through CYP3A4-mediated oxidative metabolism as well as UGT1A9-mediated glucuronidation. Up to eight metabolites of sorafenib have been characterized. Five of them have been determined in plasma. Pyridine N-oxide, the main circulating metabolite of sorafenib in plasma, demonstrates similar *in vitro* potency as sorafenib and accounts for about 9–16% of circulating analytes at steady state. Pharmacodynamic data

Table 2. Management according to renal, hepatic and cardiac comorbidity of the different FLT3 inhibitors.

FLT3 INHIBITOR	RENAL FAILURE	LIVER FAILURE	CARDIAC DYSFUNCTION
Midostaurin	- Mild or moderate: no dose adjustment. - Severe: no experience	- Child-Pugh A or B: no dosage adjustment – Child-Pugh C: no experience	- QTc interval > 500 ms: suspend - QTc interval 470–500 ms: reduce to 50 mg q.o.d
Sorafenib	- Mild, moderate or severe: no dose adjustment. - No data in dialysis patients	- Child-Pugh A or B: no dosage adjustment – Child-Pugh C: no experience	Periodic monitoring of ECG and electrolytes (magnesium, potassium, calcium) in patients at risk of developing QT interval prolongation
Gilteritinib	- Mild or moderate: no dose adjustment. - Severe: no experience	- Child-Pugh A or B: no dosage adjustment – Child-Pugh C: no experience	QTc interval >500 ms: Interrupt; when QTc interval returns to within 30 msec of baseline or ≤480 ms, resume therapy at a reduced dose of 80 mg q.o.d. QTc interval increased by >30 ms on ECG on day 8 of cycle 1: Confirm on day 9. If confirmed, consider dose reduction to 80 mg q.o.d.
Quizartinib	No data in patients with glomerular filtration rate lower than 25 ml/min	No data in patients with Child-Pugh B or C	QT interval prolongation: consider drug reduction
Crenolanib	No data	No data	No data

suggest that sorafenib N-oxide has a higher affinity for the FLT3 receptor than its parent compound.

3.2. Toxicity

Sorafenib toxicities include cardiovascular events (ischemia, infarction, QT prolongation), hemorrhages, hypertension, dermatological toxicity (hand-foot syndrome or epidermal necrolysis), gastrointestinal perforation (less than 1%) and liver toxicity [43]. The most common adverse reactions to sorafenib are hand-foot skin reaction (palmar-plantar erythrodysesthesia) and rash. Other frequent adverse reactions are diarrhea, fatigue, alopecia and infection. These symptoms are usually Grade 1 and 2 according to CCT (Common Toxicity Criteria – Common Toxicity Criteria) and, in general, appear during the first six weeks of treatment with sorafenib. Overall, sorafenib-related toxicity is generally mild (grades 1–2) and manageable with supportive care, but in severe or persistent cases it might be necessary to temporarily interrupt the treatment, to modify sorafenib dose or even to permanently discontinue sorafenib administration [43].

Cardiovascular toxicity associated with sorafenib is mainly linked to its inhibition of VEGFR, interfering with normal angiogenesis. In the TARGET and SHARP studies, the incidence of any grade hypertension was 17 and 5%, respectively, and a 4% rate of grade 3 or 4 hypertension was observed in the TARGET study [44–46]. Arterial hypertension increases the risk of myocardial infarction and cerebrovascular events, but these effects are rare during sorafenib treatment (3% and less than 1%, respectively). Hypertension is usually mild to moderate, occurs early in the course of treatment (especially in the first six weeks), and is amenable to management with standard antihypertensive therapy. Blood pressure should be monitored on a weekly basis at the beginning of therapy, and regularly thereafter. Other cardiovascular side effects were rare: cardiac failure (<1%), arrhythmia (<1%) or hypertensive crisis (<1%) [47]. Another off-target effect related to sorafenib could be hand-foot skin reaction, since some authors postulate that secretion of sorafenib into the eccrine glands results in direct toxicity to the skin [48–50]. However, no clear evidence has demonstrated that sorafenib is secreted by the eccrine glands, making this theory unlikely. It has also been postulated that sorafenib-induced hypothyroidism might be related to VEGFR inhibition, by preventing binding of VEGF to normal thyroid cells, and/or impairing thyroid blood flow, which results in thyroiditis [51].

In a double-blind, randomized, placebo-controlled study, the incidence of cardiac ischemia/infarction events during treatment in the sorafenib group (4.9%) was higher than that in the placebo group (0.4%). In another study, the incidence of cardiac ischemic/infarction events during treatment was 2.7% in the sorafenib group compared to 1.3% in the placebo group. Patients with recent myocardial infarction or unstable coronary artery disease were excluded from these trials. In patients who develop cardiac ischemia and/or infarction, a temporary or permanent discontinuation of sorafenib should be considered [43]. Sorafenib-related cardiotoxicity has been known for long, and therefore most AML trials excluded patients with heart disease or uncontrolled hypertension, which probably reduced the rate of cardiac toxicity in some trials [41]. Therefore, sorafenib-mediated cardiotoxicity should be considered in the real-world setting.

Adverse events in patients treated with sorafenib and warfarin in the form of rare bleeding events or prolongation of the International Normalized Ratio (INR) have been reported. For this reason, in patients taking warfarin or phenprocoumon concomitantly, changes in prothrombin time, INR and bleeding signs should be monitored regularly [43].

3.3. Role in different AML clinical settings

Sorafenib has not been extensively studied in the context of AML induction, but *Ravandi et al*. conducted a phase I/II trial to determine the efficacy and toxicity of the combination of sorafenib, cytarabine, and idarubicin in patients with acute myeloid leukemia (AML) <65 years. They observed that grade 3 adverse events possibly related to sorafenib during induction included hyperbilirubinemia, elevated transaminases, diarrhea, rash, pancreatitis, colitis, pericarditis, hand and foot

syndrome and elevated creatinine, which are similar to the toxicities seen in the posttransplant setting [52].

Results of the randomized phase II SORMAIN study indicate that although post-transplant maintenance with sorafenib (dose 400 mg *bid* during 24 months) was generally well tolerated, the incidence of acute and chronic GvHD was the most frequent grade 3 or higher adverse event (76.8% in the sorafenib arm vs 59.8% in the placebo group) [41]. Results from another open-label, randomized phase 3 trial evaluating the efficacy and tolerability of sorafenib maintenance post-transplantation in patients with FLT3-ITD AML were published. These results confirm a lower relapse rate and the same overall rate of adverse events compared to controls. The most frequent serious adverse events with sorafenib were cutaneous and hematological toxicity. Interestingly, the incidence of acute and chronic GVHD was similar in the sorafenib and control arms (23% vs 21% in acute GVHD; 18% vs 17% in chronic GVHD, respectively) [45].

3.4. Drug interactions

Co-administration with CYP3A4 inhibitors (such as ketoconazole) could affect its efficacy due to the reduced transformation in its active metabolite [44]. At the same time, it is unknown whether this inhibition triggers an increase of other metabolites that may modify its toxicity profile, so caution should be exercised since the optimal dose in the context of CYP3A4 inhibition is uncertain. On the other hand, CYP3A4 inducers such as rifampicin, carbamazepine, phenytoin, phenobarbital, dexamethasone and *Hypericum perforatum*, also known as St. John's Wort, may also increment the metabolism of sorafenib and therefore reduce sorafenib concentrations [43].

3.5. Off-target toxicities

Due to off-target VEGF inhibition, sorafenib can promote the formation of arterial dissections and/or aneurysms in patients with or without hypertension. Before initiating treatment with sorafenib, this risk should be carefully assessed in patients with risk factors such as history of aneurysm or hypertension [43].

3.6. Dose adjustments

Sorafenib can prolong the QT/QTc interval, which may increase the risk of developing ventricular arrhythmias. Therefore it should be used with caution in patients who have developed or are at risk of developing QTc prolongation (patients treated with a high cumulative dose of anthracycline, patients with congenital long QT syndrome, patients who are taking certain antiarrhythmic drugs or other drugs associated with a prolongation of the QT interval, and those with electrolyte disturbances such as hypocalcemia, hypokalaemia, or hypomagnesemia). When sorafenib is used in these patients, periodic monitoring of ECGs and electrolytes (potassium, magnesium, calcium) should be considered [43] (Table 2).

Patients with mild, moderate or severe renal impairment do not require dose adjustment. In patients requiring dialysis there is no available data. Monitoring of fluid and electrolyte balance is recommended in patients at risk of renal failure. No dose adjustment is required in patients with mild to moderate hepatic impairment (Child-Pugh A or B). No data are available in patients with severe hepatic failure (Child-Pugh C) [43].

4. Gilteritinib

4.1. Pharmacokinetics and pharmacodynamics

Gilteritinib is a pyrazinecarboxamide derivative that has shown potent and selective inhibitory activity of both FLT3-ITD and FLT3-TKD mutations. Gilteritinib has also inhibitory activity against EML4-ALK and Axl (a tyrosine kinase involved in the maintenance of constitutive phosphorylation of FLT3-ITD and whose activation has been described as a possible mechanism of secondary resistance to FLT3 inhibitors [53,54] (Table 1). The maximum plasma concentration is observed after 4 to 6 hours of oral administration. Food does not significantly affect its absorption. It is extensively distributed outside the plasma, which could indicate a wide tissue distribution. *In vivo*, human plasma protein binding is approximately 90% and it primarily circulates bound to albumin [55]. Gilteritinib is mainly metabolized by CYP3A4 and it is a substrate for P-glycoprotein.

Table 3. Recommendation for dose adjustment of each FLT3 inhibitor based on co administration with other drugs with metabolism by PYP3A4.

	MIDOSTAURIN	SORAFENIB	GILTERITINIB	QUIZARTINIB	CRENOLANIB
Rifampicin (strong CYP3A4 inducer)	Avoid concurrent use	Avoid concurrent use	Avoid concurrent use	Avoid concurrent use	No data available. Use with caution (crenolanib is metabolized by CYP450).
Fluconazole (moderate CYP3A4 inducer)	Dose adjustment not required	Dose adjustment not required	Dose adjustment not required	Dose adjustment not required	No data available. Use with caution (crenolanib is metabolized by CYP450).
Itraconazole/ Posaconazole (strong CYP3A inhibitor)	Consider alternative therapy; if concomitant use unavoidable, monitor closely for midostaurin-related toxicity	Not studied, but probably dose adjustment not required (based on Itraconazole data)	Consider alternative therapy; if concomitant use unavoidable, monitor closely for gilteritinib-related toxicity	Reduce dose to 30 mg daily	No data available. Use with caution (crenolanib is metabolized by CYP450).

4.2. Efficacy

Gilteritinib has been approved by the FDA and EMA for the treatment of patients with refractory or relapsed *FLT3*^{mut} AML. The efficacy of gilteritinib in refractory or relapsed *FLT3*^{mut} AML was demonstrated in the randomized, multicenter, phase III ADMIRAL trial, that compared gilteritinib at a -120 mg/m2 daily dose until progression versus salvage chemotherapy (19.9% of patients included in the study had relapsed after allogeneic SCT). The two primary endpoints were OS and the percentage of patients who had complete remission with partial or full hematologic recovery. Secondary end points included the percentage of patients who had achieved remission and event-free survival. Median OS was 10.4 months in the gilteritinib group and 6.9 months in the chemotherapy group (HR for death: 0.99; 95% CI: 0.63 to 1.55). In the gilteritinib group, 34% of the patients achieved complete remission with partial or full hematologic recovery, compared with 15.3% in the chemotherapy group [56]. Currently, numerous clinical trials of gilteritinib are underway to study its role in various settings such as first-line, maintenance, rescue or consolidation.

4.3. Toxicity

Gilteritinib is generally well tolerated. In the ADMIRAL trial, the incidence of all exposure-adjusted adverse events was higher in the chemotherapy group than in the gilteritinib group, including those that were considered by the investigator to be drug-related. Considering adverse events that occurred during the first 30 days of treatment, similar results were obtained in both groups, except for elevations of the liver aminotransferase levels, which were slightly higher in the gilteritinib group. In the gilteritinib group, the most common grade ≥3 adverse events were febrile neutropenia (45.9%), anemia (40.7%), and thrombocytopenia (22.8%), which were also the most common grade ≥3 gilteritinib-related adverse events according to the investigators. The incidence of grade ≥3 exposure-adjusted adverse events was 42.44 events per patient-year in the chemotherapy group and 19.34 events per patient-year in the gilteritinib group. QT interval prolongation related to gilteritinib occurred in 4.9% of patients, but only 1 patient (0.4%) had a maximum post-baseline increase in the mean corrected QT interval above 500 msec [56]. In other clinical studies, the most common adverse events related to Gilteritinib consisted of diarrhea (16%), anemia (33%), fatigue (15%) and elevated liver function tests (elevated AST 13%, elevated ALT 10%). The most common grade 3–4 adverse events developed were neutropenia (8.2%), anemia (24.4%), thrombopenia (12.8%), sepsis (14%), and pneumonia (12%) [55].

Special caution should be taken due to the possibility of developing a differentiation syndrome that in extreme cases could be fatal. Clinical findings and symptoms of differentiation syndrome include fever, dyspnea, weight gain, pleuropericardial effusion, pulmonary edema, peripheral edema, hypotension, renal dysfunction and rash. When suspected, corticosteroid therapy and hemodynamic monitoring should be started until resolution of symptoms. If severe symptoms and/or signs persist for more than 48 hours after initiation of corticosteroids, Gilteritinib should be discontinued until symptoms and signs decrease in severity. After resolution of symptoms, corticosteroids can be gradually reduced and should be administered for at least 3 days [55].

Posterior reversible encephalopathy syndrome (PRES) cases in patients treated with gilteritinib have been described. PRES must be suspected in case of rapidly evolving neurologic symptoms, like seizures, confusion, headache and other neurological and visual alterations, with or without changes in mental status and/or hypertension. If PRES is suspected, brain imaging should be performed, preferably magnetic resonance imaging. In these cases, it is recommended to discontinue treatment with Gilteritinib [55].

At the moment, it has not been possible to relate these adverse effects to off-target mechanisms, although it is true that more studies oriented to this issue are needed to better identify the mechanisms related to gilteritinib toxicities, especially PRES and differentiation syndrome.

4.4. Drug interactions

Gilteritinib is mainly metabolized by CYP3A4 and it is a substrate for P-glycoprotein, so potential drug interactions must be considered, which is similar to those described with midostaurin and sorafenib. Co-administration with strong inducers should be avoided. In the case of CYP3A4 inhibitors, if such association cannot be avoided, extreme precautions should be taken to avoid adverse reactions. Gilteritinib elimination is mainly fecal [55].

4.5. Dose adjustments

Gilteritinib, like midostaurin or sorafenib, may prolong QT interval, specially in the first two months of treatment. Therefore, an ECG should be performed before starting treatment, on days 8 and 15 of cycle 1, and before starting the next three cycles of treatment. In patients with relevant cardiac disease, caution is advised. Hypomagnesemia and hypokalaemia may increase the risk of QT prolongation and should therefore be corrected before and during treatment. If a QTc interval increase >30 msec on ECG on day 8 of cycle 1 is detected, it must be confirmed on day 9 and, if confirmed, a dose reduction to 80 mg q.o.d should be considered. Gilteritinib must be discontinued in patients with a QTc by Fredericia >500 msec [55].

No dose adjustments are required in patients with mild or moderate renal impairment. There is no data available in patients with severe renal failure, so gilteritinib is not recommended in these patients. No dose adjustment is required in patients with mild to moderate (Child-Pugh A or B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic failure, there is no available data [55] (Table 2).

5. Quizartinib

5.1. Pharmacokinetics and pharmacodynamics

Quizartinib is a potent second-generation type 2 FLT3 inhibitor that has also inhibitory activity against PDGFR and KIT

(Table 1). Quizartinib maximum concentration is reached within 4 hours after oral administration. It has a long terminal half-life (3.5 hours) and its elimination is mainly fecal [57]. It is extensively metabolized through CYP3A4, which must be taken into account when co-administered with inducers or inhibitors of this cytochrome.

5.2. Efficacy

The role of quizartinib in relapsed/refractory FLT3-ITD AML was evaluated in the multicenter phase III QuANTUM-R trial (NCT02039726), which randomized 367 patients with relapsed/refractory *FLT3*^{mut} AML after standard therapy in a 2:1 ratio to receive either quizartinib 60 mg q.o.d. or salvage chemotherapy. Primary endpoint of the study was overall survival, while secondary and exploratory endpoints were event-free survival, CRc rate and duration, and transplantation rate. Quizartinib prolonged overall survival compared with chemotherapy (median overall survival: 27.0 weeks versus 20.4 weeks, 1-year overall survival rate: 27% versus 20%; p = 0.0177) [58]. Despite these results, quizartinib was not approved for relapsed/refractory AML by neither the FDA nor the EMA because of doubts about generalizability of the trial design [59]. A wide variety of trials with quizartinib are currently active in different settings for the treatment of AML.

5.3. Toxicity

Quizartinib's most common adverse events include nausea, anemia, fatigue, vomiting, diarrhea, febrile neutropenia and QT interval prolongation. However, it is generally well tolerated with manageable toxicity, and its main initial limitation (considerable rates of QT interval prolongation) decrease significantly after reduciding quizartinib dose without impairing its anti-leukemic efficacy [48]. In the QuANTUM-R trial (NCT02039726), dose reduction was required in 32% of patients in the quizartinib group; motivated by adverse events (12%), QT interval prolongation (9%), concomitant CYP3A4 inhibition (6%) or other reasons (5%). Grade ≥3 adverse events evidenced in at least 5% of patients in the quizartinib group consisted of hematological events, infections, electrolyte abnormalities, fatigue and dyspnea. Regarding non-hematological grade 3–5 events, the most common were septic shock or sepsis (19% for both quizartinib and chemotherapy), pneumonia (12% vs 9%) and hypokalemia (12% vs 9%). Treatment-emergent adverse events leading to quizartinib discontinuation were observed in 8% patients; the most common reasons were pneumonia (2%), intracranial hemorrhage (2%), graft-versus-host disease (2%) and septic shock or sepsis (2%) [58].

There is scarce evidence available about the possible off-target toxicities that quizartinib can cause, but as with other drugs with similar characteristics, myelosuppression could be linked to its inhibitory activity against c-KIT.

5.4. Drug interactions

Co-administration of quizartinib with drugs that prolong the QT/QTc interval and moderate or strong CYP3A inducers was prohibited in the QuANTUM-R trial (except when considered by the investigator as essential for patient care). Avoidance of strong CYP3A inhibitors was recommended but not prohibited; however, if they were used, quizartinib dose adjustments were required. Weak or moderate CYP3A inhibitors, such as fluconazole, were allowed without dose reduction.

5.5. Dose adjustments

Quizartinib can prolong the QT interval. If a QT prolongation grade 2 is detected, quizartinib dose should be reduced (if it was previously reduced, quizartinib must be interrupted for 4 days and reintroduced at the previous dose if QTc by Fredericia returned to within 30 ms of baseline or </ = 450 ms); in grade 3 QT prolongation, quizartinib must be interrupted for at least 14 days and, in the case of grade 4, it must be discontinued [60].

Patients with a glomerular filtration rate lower than 25 ml/min were excluded from the QuANTUM-R trial, as well as those with clinically relevant liver disease, hepatitis B or C. Therefore there is no experience in these circumstances (Table 2).

6. Crenolanib

6.1. Pharmacokinetics and pharmacodynamics

Crenolanib was originally developed as a selective PDGFR inhibitor, and it also exhibits c-Kit inhibitory activity (Table 1), albeit with a much lower potency than quizartinib, which appears to be an advantage due to the fact that c-Kit inhibition has been associated with dose-limiting side effects such as myelosuppression and QT interval prolongation. Additionally, crenolanib is a potent inhibitor of FLT3-D835, which is one of the main mechanisms of resistance to FLT3 inhibitors. Preliminary data suggest that crenolanib may overcome common resistance mechanisms that have been seen with type II inhibitors, while having greater FLT3 inhibitory potency than other type I inhibitors. Clinical and pharmacokinetic data indicate that it is metabolized by cytochrome P450 and its half-life is approximately 8 hours, requiring a three-times a day administration [14].

6.2. Efficacy

Crenolanib is a potent type 1 FLT3 inhibitor with activity against both FLT3-ITD and FLT3-TKD. The efficacy of crenolanib is being tested in a double-blinded, placebo-controlled, phase 3 trial in *FLT3*^{mut} relapsed/refractory AML (NCT02298166). The primary endpoints are event free survival and OS [61]. Recruitment has already been terminated, and the results of this clinical trial are highly awaited. Crenolanib is currently under development with other ongoing phase II and III trials.

6.3. Toxicity

In general, crenolanib is well tolerated, with the most frequent adverse events being nausea and other gastrointestinal toxicities, elevation of liver enzymes and fluid retention [50]. Little

data on crenolanib safety exist among patients with abnormalities in cardiac, liver or kidney function tests (Table 2). In fact, patients with ejection fraction <45% confirmed by echocardiography, creatinine levels >1.5 upper limit of normality, total bilirubin > upper limit of normality or AST or ALT >2 upper limit of normality have been excluded from the phase 3 study under development [61].

There are very few pieces of literature about crenolanib off-target effects. It has been postulated that the relatively limited activity of crenolanib against c-KIT may offer a unique advantage of this drug over others in this class causing less suppression of bone marrow function [14]

7. Conclusion

The recent clinical development of various FLT3 inhibitors for the treatment of *FLT3*^{mut} AML has proved to be an effective therapeutic strategy. Since the approval of midostaurin in combination with standard chemotherapy in adults with newly diagnosed *FLT3*^{mut}AML, numerous drugs against the FLT3 mutant protein have been developed, some of which are still under investigation in various trials. At this moment, only gilteritinib has also been approved for use in a different clinical setting of *FLT3*^{mut} AML. It is expected that in a short time, new drugs and new indications will arise in different clinical settings of AML.

However, FLT3 inhibitors have unique toxicities and drug–drug interactions that need to be carefully considered. For example, QTc interval prolongation and drug interactions with inducers or inhibitors of CYP3A4 are common to all FLT3 inhibitors, whereas gastrointestinal toxicity is more characteristic of midostaurin. Importantly, drug interactions with posaconazole (a strong CYP3A4 inhibitor) are particularly relevant, as this is the standard of care antifungal agent used for prophylaxis during induction treatment of AML [15]. The management strategy for each drug in this case needs to be standardized (Table 3). Overall, many such adverse events might be prevented with the development of novel agents with greater specificity for FLT3.

8. Expert opinion

8.1. Role of FLT3 inhibitors in newly diagnosed AML

An increasing interest exists in the use of FLT3 inhibitors as first line therapy for *FLT3*^{mut} AML [62]. Several studies are currently analyzing the addition of these inhibitors to standard chemotherapy in young patients with newly diagnosed AML. This rapid expansion is mainly motivated by the compelling results of the RATIFY trial, explained above [11].

Several other more selective FLT3 inhibitors (gilteritinib, quizartinib, crenolanib) are being tested in the upfront setting in diverse trials with satisfactory preliminary results [63–68]. For example, in a dose escalation trial of quizartinib in combination with induction and consolidation chemotherapy, high remission rates have been reported and drug-related toxicities were manageable [66]. Importantly, no unexpected or significant additional toxicities were observed with the combination regimen, and the main dose limiting toxicities were pericardial effusion (grade 4), decreased platelet count, febrile neutropenia, pericarditis (grade 3) and QT interval prolongation (grade 3).

The combination of FLT3 inhibitors with hypomethylating agents for patients with *FLT3*^{mut} AML who are ineligible for intensive chemotherapy is another interesting area of development. Promising results were obtained with the frontline combination of 5-azacitidine and the multi-kinase inhibitor sorafenib in *FLT3*^{mut} AML patients, achieving high remission rates (including a 70% of complete responses with incomplete hematologic recovery) and a median overall survival of 8.3 months (9.2 months among responders) with an acceptable toxicity profile which consisted of diarrhea (22%), hyperbilirubinemia (22%), fatigue (22%) and nausea (19%) as the most common adverse events. Neutropenic fever (26%) and infections (26%) were the most common grade 3/4 adverse events [69]. The randomized, open-label, three-arm, phase 2/3 LACEWING trial (NCT02752035) is currently studying the effectiveness of gilteritinib alone or in combination with 5-azacitidine *vs* 5-azacitidine alone in patients ≥18 years with newly diagnosed *FLT3*^{mut} AML ineligible to receive intensive induction chemotherapy [70]. Encouraging findings from the safety cohorts indicate good tolerability of the drug combination and an overall response rate of 80% (67% complete responses and 13% partial responses) [71].

8.2. Maintenance therapy after allogeneic SCT

Maintenance strategies with FLT3 inhibitors after allogeneic SCT have been studied in different clinical trials. The RADIUS trial was a randomized, open-label, phase 2 exploratory trial designed to investigate if the addition of midostaurin to standard of care after allogeneic SCT could impact the risk of relapse in *FLT3*^{mut} AML patients. A 46% reduced risk of relapse was detected in the midostaurin arm, but the study was inadequately powered to detect a statistically significant difference [72]. Another phase 2 trial was performed to determine the feasibility of adding midostaurin to intensive chemotherapy followed by allogeneic SCT followed by single-agent maintenance therapy for 12 months. The trial objective was the event-free survival rate compared with historical FLT3-ITD mutated AML controls. Median duration of treatment after allogeneic SCT was 9 months, and premature termination was mostly due to non relapse causes (e.g. infections and gastrointestinal toxicity). Propensity score-weighted analysis revealed a significant improvement of event-free survival by midostaurin (hazard ratio, 0.58; 95%CI, 0.48–0.70; $P < .001$), which was also present among older patients (hazard ratio, 0.42; 95%CI, 0.29–0.61). Midostaurin maintenance therapy induced some degree of toxicity, particularly after allogeneic SCT, due to anticipated interactions between immunosuppressants & anti-infective agents with midostaurin. However, the landmark analysis in this study established at day 100 after transplant favors maintenance therapy after allogeneic SCT both in terms of event free and OS [16]. The SORMAIN trial was a randomized, double-blind, placebo-controlled and multicenter study designed to study the efficacy of sorafenib maintenance after allogeneic SCT in *FLT3*^{mut} AML patients in complete remission [41]. After a median follow-up of

41.8 months, median relapse free survival in the placebo group was 30.9 months and not reached in the sorafenib group, which corresponded to a 2-year relapse free survival of 53.3% and 85.0%, respectively. Another open-label, randomized phase 3 trial investigated the efficacy and tolerability of sorafenib maintenance posttransplantation in FLT3-ITD AML patients. The results of this trial evidenced a significant reduction in 1-year cumulative incidence of relapse in the sorafenib arm compared to controls (7.0% vs 24.5%, hazard ratio 0 · 25, 95% CI 0 · 11–0 · 57; p = 0 · 0010) with acceptable tolerance and safety [45].

These results pose a dilemma for clinicians, as patients with FLT3-ITD AML have high rates of relapse after allogeneic SCT, and most investigators agree that agents like midostaurin or sorafenib may benefit some patients [73,74]. The appearance of the relapse-free survival curves in the aforementioned trials suggests that this approach may not cure AML but rather just delay relapse. However, with current methods, even if maintenance therapy can benefit some patients in terms of delaying repase, we are currently unable to identify those patients in an accurate way. Treatment of all to benefit a minority would be a reasonable strategy if the available agents had much less toxicity than that seen with either midostaurin or sorafenib [75]. For this reason, data from randomized trials to better establish the role of maintenance therapy with more selective agents to prevent AML recurrence is an unmet medical need. In this line, the randomized, double-blind, placebo-controlled multicenter MORPHO trial (NCT02997202) is currently evaluating the effect of gilteritinib maintenance after allogeneic SCT in FLT3-ITD mutated AML [76]. With an expected enrollment of 532 patients, this will be the most powerful trial to analyze the role of FLT3 inhibitors as posttransplantation maintenance and its results can be decisive to determine the ultimate role for post-SCT maintenance therapy in FLT3-ITD AML.

Another issue of consideration is the high risk of developing acute graft-versus-host disease after allogeneic SCT, which peaks in the time period immediately following transplantation (<100 days). As a result, immunosuppressive therapy is recommended. While there is no universally accepted standard of care regimen, most institutions utilize a two-drug therapy, with one agent being a calcineurin inhibitor [77]. The most commonly used prophylactic agents are cyclosporine and tacrolimus. Cyclosporine is extensively metabolized by the CYP3A enzyme system in the liver and can be altered by coadministration with a variety of medications [78]. Tacrolimus undergoes similar metabolism, and even mild to moderate CYP3A inhibitors or inducers can substantially alter tacrolimus whole blood concentrations. When evaluating the metabolic pathways of midostaurin, it was noted that midazolam's area under the curve (AUC), a sensitive CYP3A substrate, was not affected following 4 days of midostaurin administration. However, *in vitro* studies evidenced that midostaurin does inhibit multiple cytochrome P450 isoforms (including the 3A isoform) [79]. Currently, there is little evidence available on the possible interaction between midostaurin and calcineurin inhibitors, although cases of relevant interactions have been described [80]. Therefore, careful monitoring of serum trough levels of the immunosuppressive drugs after initiation of midostaurin therapy is recommended.

8.3. FLT3 inhibitors in relapsed AML after allogeneic SCT

FLT3^{mut} AML patients who relapse after an allogeneic SCT have a poor prognosis, with 2-year survival rates below 20% independently of the selected therapy [81]. The use of new FLT3 inhibitors is of great promise for these patients, both in monotherapy and in combination with chemotherapy. Currently, only gilteritinib has been approved as monotherapy for these patients. In the same line, crenolanib is currently under study and quizartinib appraisal by regulatory agencies has been negative. Additionally, off-label use of sorafenib has been widely used on the basis of a retrospective analysis of the European Bone Marrow Transplantation (EBMT) Acute Leukemia Working Party.

The results obtained from ongoing clinical trials are especially important in order to diversify the therapeutic armamentarium in relapsed and refractory AML patients, for whom there is currently no effective therapy. Due to the different safety profile that exists among these drugs, a patient-oriented drug selection might be possible in the future that will limit the possibility of significant adverse events. Thus, for example, in a patient with a history of neurological involvement by AML, gilteritinib might be avoided due to its relationship with the development of PRES. Furthermore, due to the theoretical higher specificity of crenolanib against FLT3 mutant protein and its lower inhibitory activity against c-kit, it is expected that this drug will have a lower capacity to prolong the QT interval, so it could be an agent especially indicated in patients who are taking certain antiarrhythmic drugs or other drugs associated with QT interval prolongation, patients with congenital QT syndrome or patients with electrolyte disturbances such as hypokalaemia, hypocalcemia or hypomagnesemia.

8.4. Role of FLT3 inhibitors in relapsed or refractory AML in the elderly patient

Elderly and unfit patients who are refractory or relapse after the first line of therapy with hypomethylating agents have a dismal prognosis. In this subgroup, upfront sorafenib does not increase overall survival in combination with first line chemotherapy due to increased toxicity [82]. However, encouraging results of a phase 1/2 single-arm study testing the combination of sorafenib with 5-azacitidine have been published [83]. The response rate was 46%, including 6 (16%) complete responses (CR), 10 (27%) complete responses with incomplete count recovery (CRi) and 1 (3%) partial response. The majority (53%) of patients experienced grade <3 adverse effects attributable to sorafenib, just 1 patient discontinued treatment because of a grade 4 adverse cardiac effect [83]. These good results should be confirmed in larger studies specifically designed for ederly populations, in order to try to identify the best drug combination depending on each patient profile. One example of this is the employment of the

Bcl-2 inhibitor venetoclax plus a hypomethylating agent, which is emerging as a potential new standard of care for the frontline treatment of older adults with newly diagnosed AML who are ineligible for intensive chemotherapy, since it has shown very promising results [84]. Nevertheless, despite the preclinical rationale for Bcl-2 inhibition in *FLT3*^{mut} AML [85], the exact role of venetoclax in this setting remains largely unknown and rationally designed combinatorial trials should be performed to evaluate this hypothesis.

8.5. Future perspectives

In our opinion, future perspectives on the role of FLT3 inhibitors in the treatment of AML are going to be focused on the development of increasingly selective inhibitors with fewer adverse reactions and selective FLT3 inhibition. Such drug innovations would be expected to be accompanied by a reduced spectrum of adverse events. Additionally, FLT3 inhibitors will be combined with other therapeutic agents (including induction and consolidation chemotherapy) and in different clinical settings (bridging for transplant, relapse/refractory setting, salvage post-transplant therapy, and as prophylactic long-term post-transplant maintenance). The definitive end-point could be to identify the ideal combination of each FLT3 inhibitor with the most synergistic treatment (standard chemotherapy, hypomethylating agents, venetoclax . . . .), taking into account the individual characteristics of each patient. Many challenges remain though, such as their difficult tolerability profile with high-dose chemotherapy in older or frail patients and their optimal timing as prophylaxis.

There are many other drugs in development for the treatment of AML (Bcl-2 inhibitors, IDH1 & IDH2 inhibitors, monoclonal antibody). A big challenge will be to understand how different molecular profiles will respond to the different drugs and possible drug combinations. An increased understanding of the genomic determinants of drug response and resistance will be necessary in order to select the right drug or drug combination, which will probably need innovative umbrella trials and extensive real-world data coupled with molecular analysis and artificial intelligence applications. In this line, as an increasing number of drugs are on the road, the combination of FLT3 inhibitors with other agents such as intensive chemotherapy or selective check-point inhibitors will eventually enable a fully personalized treatment of AML, instead of the current 3 + 7 *'one size fits it all'* paradigm [86–92].

Finally, over the next years, and mainly due to the progressive advance of *'à la carte medicine'* based on molecular targets, the ultimate goal should be to identify those AML patients who would not benefit from allogeneic SCT, as this procedure is accompanied by high morbidity and mortality [93]. Although the best outcomes in the RATIFY study were observed among patients who received midostaurin with induction and then underwent allogeneic SCT in remission [11], it is possible that the use of alternative FLT3 inhibitors or prolonged FLT3 inhibitor maintenance (e.g. beyond 1 year) may modify our current risk stratification of patients with *FLT3*^{mut} AML, particularly when other established prognostic factors are taken into consideration (e.g. type of *FLT3* mutation, *FLT3* allelic ratio and *NPM1* status). However, for the moment, the recommended approach in newly diagnosed *FLT3*^{mut} AML among fit patients remains the addition of midostaurin to intensive chemotherapy, followed by allogeneic SCT in first remission [59,94]. Prospective multicenter randomized clinical trials in this setting should be pursued.

Declaration of interest

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ORCID

Claudio Cerchione http://orcid.org/0000-0002-9104-5436
Manuel Mateo Pérez Encinas http://orcid.org/0000-0001-9943-4404

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