Are FLT3 inhibitors likely to improve *FLT3*-mutated acute myeloid leukemia in the foreseeable future?

“With the advent of new technologies for genomic analysis, such as next-generation sequencing, particularly for minimal residual disease assessment, it seems to be reasonable that the results will further improve the management of individual patients through the implementation of innovative diagnostic/prognostic systems and the development of therapeutic strategies based on the individual genomic profile.”

Sabine Kayser^{1,2} & Mark J Levis^{*,3}

First submitted: 3 January 2017; Accepted for publication: 10 January 2017;
Published online: 24 February 2017

Treatment of *FLT3*-mutated acute myeloid leukemia

Activating *FLT3* mutations are one of the most frequently affected genetic abnormalities in acute myeloid leukemia (AML) and are present in about 30–40% of newly diagnosed patients [1]. As a member of the type III receptor tyrosine kinase subfamily, including c-KIT, c-FMS and PDGFR- α/β , it is involved in proliferation and differentiation of myeloid progenitor cells [2]. In cytogenetically normal AML, internal tandem duplications of the *FLT3* gene (*FLT3*-ITDs) are associated with an unfavorable prognosis due to a high relapse rate, whereas the prognostic impact of point mutations within the tyrosine kinase domain (*FLT3*-TKDs) remains controversial [3]. Nevertheless, *FLT3*-TKDs can occur after treatment with certain *FLT3* tyrosine kinase inhibitors (TKIs) as a mechanism of resistance, thus implicating an adverse prognosis [4].

The recent results of the large, international, randomized Phase III

CALGB 10603 (RATIFY) trial have generated considerable enthusiasm in the field, in that we actually may have a new treatment option for *FLT3*-mutated AML [5]. Within this trial, the *FLT3* mutation was determined centrally prior to enrollment in one of nine academic labs around the world with results being available within 48 h. The trial was activated in May 2008 and recruitment of over 700 younger adult *FLT3*-mutated AML patients (18–60 years) was finally achieved in October 2011, necessitating a prescreening of almost 3300 AML patients for the presence of a *FLT3*-mutation – a huge logistical accomplishment. The study scheme consisted of the addition of midostaurin or placebo to standard intensive 7 + 3 induction chemotherapy as well as four cycles of high-dose cytarabine (HiDAC) as consolidation therapy. In all patients, maintenance therapy of 1 year with midostaurin or placebo according to initial randomization was intended. Although not specifically mandated, allogeneic stem cell transplantation (SCT) was

KEYWORDS

- AML • *FLT3* mutations • genetics
- leukemia • novel therapy

“Activating *FLT3* mutations are one of the most frequently affected genetic abnormalities in acute myeloid leukemia and are present in about 30–40% of newly diagnosed patients.”

¹Department of Internal Medicine V, University Hospital of Heidelberg, Heidelberg, Germany

²Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ) & Department of Internal Medicine V, University Hospital of Heidelberg, Heidelberg, Germany

³Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

*Author for correspondence: Tel.: +1 410 502 3629; Fax: +1 410 614 1005; Levisma@jhmi.edu

“The ultimate goal is to turn more of the laboratory breakthroughs into life-saving treatments.”

performed in 57% of the overall study cohort. The combination of midostaurin to intensive chemotherapy significantly improved overall survival (OS) in younger adults with *FLT3*-mutated AML with a hazard ratio of 0.77 (95% CI: 0.63–0.95; p-value = 0.008), translating into a median OS of 74.7 months for the midostaurin-arm (range: 31.7 months not reached) as compared with 25.6 months for the placebo-arm (range: 18.6–42.9 months), respectively. Interestingly, this improvement was regardless of the *FLT3* mutational status (either ITD or TKD) or the *FLT3*-ITD allelic ratio [5]. Based on these results, the US FDA granted priority review to midostaurin for the treatment of adult newly-diagnosed *FLT3*-mutated AML, setting up a possible US approval for the drug in the first half of 2017. The premarket approval application for the *FLT3* companion diagnostic, developed in collaboration with Invivoscribe Technologies, Inc. has also been accepted for review by the FDA. In Europe, the marketing authorization application for midostaurin is under review by the EMA.

Nevertheless, even in the midostaurin-arm, a significant proportion of the patients still relapsed within the first 2 years, raising the question as to whether or not more selective TKIs would be more beneficial.

Currently, there are numerous other *FLT3* inhibitors in development [6]. Very promising data have been presented at the American Society of Hematology (ASH) annual meeting in San Diego 2016 for two more selective *FLT3* TKIs: results of a Phase II trial of crenolanib in combination with intensive chemotherapy [7] as well as results of a first-in-human Phase I/II dose-escalation, dose-expansion study with gilteritinib [8].

Crenolanib is a selective and potent type I oral *FLT3* TKI, which inhibits both, *FLT3*-ITD and *FLT3*-TKD mutations [9]. It is rapidly absorbed, has a short 6–8 h half life and there is no accumulation with chronic dosing. So far, 38 adult *FLT3*-mutated AML patients (median age: 58 years, range: 19–75 years) have been enrolled within the above mentioned trial (NCT02283177) [7]. The treatment scheme is comparable to the CALGB 10603/RATIFY trial and consisted of standard 7 + 3 induction with cytarabine 100 mg/m²/d for 7 days and either daunorubicin (<60 years: 90 mg/m²; ≥60 years: 60 mg/m²) or idarubicin 12 mg/m² for 3 days. Crenolanib 100 mg three-times daily

was administered starting on day 9 until 72 h prior to next chemotherapy. Reinduction was permitted for patients with inadequate leukemia cytoreduction. Up to four courses of age-adapted consolidation consisting of six doses of HiDAC (<60 years: 3 g/m²; ≥60 years: 1 g/m²) were given, with crenolanib starting on day 7. Eligible patients could proceed to allogeneic SCT and maintenance therapy with crenolanib was offered for 1 year after HiDAC or allogeneic SCT. Complete remission or complete remission with incomplete count recovery after first and/or second induction therapy were achieved in 28/32 (88%) evaluable patients and 16 (42%) patients went on to allogeneic SCT. Crenolanib was well tolerated in combination with chemotherapy, with only six patients requiring crenolanib dose reductions (four were in patients >60 years). Most of the patients had full count recovery after first induction therapy, probably owing to the lack of c-KIT inhibition by crenolanib at clinically achievable concentrations. Median follow-up was 6 months without any relapses in *FLT3*-mutated AML so far. Though premature, the results look very promising and accrual to this trial continues. In addition, a confirmatory, multicenter, pivotal trial is underway.

Very encouraging results had also been presented on gilteritinib in relapsed/refractory AML patients (Clinicaltrials.gov: NCT02014558) [8]. Comparable to crenolanib, gilteritinib (ASP2215) is a novel, highly selective, potent oral *FLT3* inhibitor with activity against ITD and TKD mutations [10]. Within this Phase I/II trial, 252 AML patients had been enrolled. All of the patients had been intensively pretreated: 70% had at least two prior AML therapies, 29% had a prior SCT and 25% had prior TKI treatment with sorafenib most commonly used. Median age was 62 years (age range: 21–90 years) and 77% were *FLT3*-mutated (n = 194/252). The treatment consisted of single agent gilteritinib, once daily, starting with 20 mg up to 450 mg in dose escalation or concomitant dose-expansion cohorts. Maximum tolerated dose was determined to be 300 mg when two of three patients in the 450 mg cohort experienced diarrhea and/or hepatic transaminase elevation as dose-limiting toxicities. The overall response rate (ORR) was higher in *FLT3*-mutated as compared with wild-type patients (ORR: 49 vs 12%, respectively). ORR in 169 *FLT3*-mutated patients receiving ≥80 mg gilteritinib was 52% and occurred across all *FLT3* mutations (ORR for ITD: 55%; for

TKD: 17%; for both mutations: 62%, respectively). Median OS was roughly 31 weeks (range: 1.7–61 weeks) and median duration of response was 20 weeks (range: 1.1–55 weeks).

Taken together, gilteritinib was well tolerated with a high response rate in relapsed or refractory, heavily pretreated *FLT3*-mutated AML patients. The survival of these patients appears better than expected for this patient population when treated with standard therapy. Currently, a Phase III trial of oral gilteritinib 120 mg once a day versus salvage chemotherapy in patients with *FLT3*-mutated relapsed or refractory AML after first-line therapy is underway (NCT02421939).

Suggested approach to *FLT3*-mutated AML

In younger *FLT3*-mutated AML adults, the most promising approach seems to be the use of FLT3 inhibitors in combination with induction chemotherapy and/or as consolidation/maintenance therapy after allogeneic SCT. Assuming that midostaurin will get FDA approval, its use according to the CALGB 10603/RATIFY trial to treat younger adult *FLT3*-mutated AML patients seems currently to be the best approach.

Since both, a concomitant *NPM1* mutation as well as the allelic ratio of *FLT3*-ITD, have been shown to impact prognosis of cytogenetically normal *FLT3*-mutated AML, whenever possible these two characteristics should be evaluated [11–13]. Particularly in younger patients with a low allelic ratio and a concomitant *NPM1* mutation, who are minimal residual disease negative following induction chemotherapy, the possible risks associated with an allogeneic SCT should be carefully considered. These patients might be more appropriate candidates for HiDAC consolidation in combination with midostaurin followed

by TKI maintenance. Currently, it is evaluated in clinical trials, if newer, more selective TKIs might be clinically more beneficial.

Older (>75 years) *FLT3*-mutated AML patients who are not candidates for intensive therapy including allogeneic SCT should be preferentially enrolled on FLT3 TKI based trials. If no such trial is available, we recommend the combination of sorafenib (off-label) and azacytidine as published, since this regimen has been shown to induce synergistic differentiation of *FLT3*-ITD AML cells [14].

With the advent of new technologies for genomic analysis, such as next-generation sequencing, particularly for minimal residual disease assessment [15], it seems to be reasonable that the results will further improve the management of individual patients through the implementation of innovative diagnostic/prognostic systems and the development of therapeutic strategies based on the individual genomic profile. The ultimate goal is to turn more of the laboratory breakthroughs into life-saving treatments.

Financial & competing interests disclosure

S Kayser gratefully acknowledges to be supported by the Olympia-Morata program of the Medical Faculty of the University of Heidelberg. MJ Levis is supported by a grant from the NCI (NCI Leukemia SPORE P50 CA100632). He receives research funding from Novartis and Astellas. He serves as a consultant for Novartis, Daiichi-Sankyo, Astellas and Arog. S Kayser has served as a consultant for Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- 1 The Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult *de novo* acute myeloid leukemia. *N. Engl. J. Med.* 368(22), 2059–2074 (2013).
- 2 Brandts CH, Sargin B, Rode M *et al.* Constitutive activation of Akt by Flt3 internal tandem duplications is necessary for increased survival, proliferation, and myeloid transformation. *Cancer Res.* 65(21), 9643–9650 (2005).
- 3 Levis M. *FLT3* mutations in acute myeloid leukemia: what is the best approach in 2013? *Hematology Am. Soc. Hematol. Educ. Program* 2013, 220–226 (2013).
- 4 Kayser S, Levis MJ. FLT3 tyrosine kinase inhibitors in acute myeloid leukemia: clinical implications and limitations. *Leuk. Lymphoma* 55(2), 243–255 (2014).
- 5 Stone RM, Mandrekar S, Danford BL *et al.* The multi-kinase inhibitor midostaurin prolongs survival compared with placebo in combination with daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and as maintenance therapy in newly diagnosed acute myeloid leukemia (AML) patients age 18–60 with FLT3 mutations: an international prospective randomized placebo-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). *Blood* 126(22), Abstract 6 (2015).
- 6 Konig H, Levis M. Targeting FLT3 to treat leukemia. *Expert Opin. Ther. Targets* 19(1), 37–54 (2015).
- 7 Wang ES, Stone RM, Tallman MS, Walter RB, Eckardt JR, Collins R. Crenolanib, a type I FLT3 TKI, can be safely combined with cytarabine and anthracycline induction chemotherapy and results in high response rates in patients with newly diagnosed *FLT3*

- mutant acute myeloid leukemia. *Blood* 128(22), Abstract 1071 (2016).
- 8 Perl AE, Altman JK, Cortes JE *et al.* Final results of the chrysalis trial: a first-in-human Phase 1/2 dose-escalation, dose-expansion study of gilteritinib (ASP2215) in patients with relapsed/refractory acute myeloid leukemia. *Blood* 128(22), Abstract 1069 (2016).
- 9 Galanis A, Ma H, Rajkhowa T *et al.* Crenolanib is a potent inhibitor of FLT3 with activity against resistance-conferring point mutants. *Blood* 123(1), 94–100 (2014).
- 10 Lee LY, Hernandez D, Rajkhowa T, *et al.* Pre-clinical studies of gilteritinib, a next-generation FLT3 inhibitor. *Blood* 129(2), 257–260 (2017).
- 11 Pratorcorona M, Brunet S, Nomdedéu J *et al.* Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden *FLT3-ITD* mutation and concomitant *NPM1* mutation: relevance to post-remission therapy. *Blood* 121(14), 2734–2738 (2013).
- 12 Schlenk RF, Kayser S, Bullinger L *et al.* Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. *Blood* 124(23), 3441–3449 (2014).
- 13 Ivey A, Hills RK, Simpson MA *et al.* Assessment of minimal residual disease in standard-risk AML. *N. Engl. J. Med.* 374(5), 422–433 (2016).
- 14 Ravandi F, Alattar ML, Grunwald MR *et al.* Phase II study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood* 121(23), 4655–4662 (2013).
- 15 Levis M, Miller J, Xie Z, McClain V, Carson A, Stenzel T. A novel next-generation sequencing based assay for FLT3/ITD mutations is sensitive and specific and can be used to detect minimal residual disease in AML patients. *Haematologica* Abstract P568 (2016).