Best Practice & Research Clinical Haematology 32 (2019) 101103

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Beyond midostaurin: Which are the most promising FLT3 inhibitors in AML?

Eunice S. Wang

Leukemia Service, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

ARTICLE INFO

Keywords:
Acute myeloid leukemia
AML
Crenolanib
FLT3
Gilteritinib
Midostaurin
Sorafenib
Tyrosine kinase inhibitors
Quizartinib

ABSTRACT

Mutations of *FLT3* occur in around a third of acute myeloid leukemia (AML) patients and are associated with poor outcomes. Multiple targeted tyrosine kinase inhibitors (TKI) have been developed with different selectivity and potency for *FLT3* mutant clones. Indications for which FLT3 inhibitor to use depend on the clinical setting and disease status. Patients with relapsed or refractory AML benefit from a different TKI than those with de novo AML or following stem cell transplant. Moreover, each FLT3 TKI displays a different toxicity and inhibitory profile and may be most useful in patients with varying comorbidities and types of *FLT3* mutations.

Introduction

FLT3 mutations constitute one of the most common gene mutations identified in acute myeloid leukemia (AML) and occur in approximately 20%–30% of newly diagnosed patients [1]. *FLT3* mutations are typically considered secondary or driver mutations resulting in constitutive activation of FLT3 kinase and activation of multiple downstream signaling pathways promoting rapid proliferation. Two types of *FLT3* mutations have been described. Internal tandem duplication (ITD) mutants are most frequent and have been definitively associated with shorter relapse-free survival (RFS), overall survival (OS), and clinically more aggressive disease in younger patients with AML. In contrast, mutations in the tyrosine kinase domain (TKD) are infrequent and do not appear to have the same prognostic impact as ITD variants [2].

Numerous FLT3 tyrosine kinase inhibitors (TKIs) have been specifically developed over the course of the last several years for treatment of patients with *FLT3* mutant disease. These range from the first-generation multikinase inhibitors, which were actually repurposed broad spectrum kinase inhibitors originally developed for solid tumors, to the rational development of second-generation inhibitors chosen specifically for their ability to potently and selectively inhibit mutant FLT3 kinase (Table 1) [3–6]. The first- and second-generation FLT3 TKIs differ vastly in their spectrum of activity against a broad range of kinases and in their potency to inhibit FLT3 kinase specifically.

Important differences are noted between type I (eg, sunitinib, midostaurin, lestaurtinib, crenolanib, gilteritinib) and type II (eg, sorafenib, ponatinib, quizartinib) TKIs in their ability to inhibit both the active and inactive formulations of mutant kinase. This results in significant differences of these kinase inhibitors to inhibit FLT3 TKD and ITD mutations [7]. Type I inhibitors bind active and inactive receptors near the activation loop or the ATP binding pocket and target ITD and TKD mutations. Type II inhibitors bind inactive FLT3 receptors near the ATP binding domain and do not target TKD mutants.

E-mail address: Eunice.Wang@RoswellPark.org.

https://doi.org/10.1016/j.beha.2019.101103

Table 1
FLT3 TKIs differ based on selectivity and potency for mutant *FLT3*.

	Other Kinases	IC50 (plasma)
Lestaurtinib	JAK2, TrkA	700 nM
Midostaurin	cKIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib	cKIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	cKIT, PDGFR, RET	18 nM
Crenolanib	PDGFR	48 nM
Gilteritinib	AXL	43 nM

Clinical trials

The appropriate clinical setting for FLT3 inhibitors has ranged across the entire spectrum of AML therapy. In relapsed or refractory AML, the second-generation FLT3 inhibitors, gilteritinib and quizartinib, have been used as monotherapy, and crenolanib has been used in combination with salvage chemotherapy. In de novo AML, many TKIs have been evaluated in combination with cytarabine and anthracycline (7 + 3) based induction and consolidation (eg, midostaurin, crenolanib, gilteritinib, quizartinib) as well as with low-dose hypomethylating chemotherapy (gilteritinib, midostaurin, quizartinib, crenolanib). For maintenance therapy, FLT3 TKIs (midostaurin, sorafenib, gilteritinib) have been used after allogeneic stem cell transplantation.

Quizartinib is a highly potent type II inhibitor of *FLT3* ITD, CSF1R, cKIT, and PDGFR, which displays no efficacy against *FLT3* TKD mutations [4,8]. Quizartinib is given as once daily dosing with a half-life > 36 h. In the phase 3 QUANTUM-R trial [9], adult patients with *FLT3* mutant primary refractory AML or AML relapsing within 6 months of first remission were randomized. Patients could receive monotherapy with quizartinib vs salvage chemotherapy consisting of either lose-dose or high-dose regimens based on physician choice. All patients were allowed to proceed onto hematopoietic stem cell transplant. Overall, quizartinib treatment was associated with a statistically significant ($P = .0177$) improvement in overall survival (OS) over salvage chemotherapy (6.2 months vs 4.7 months, respectively). Although quizartinib demonstrated a favorable safety profile, cardiac issues, specifically QTc prolongation and myelosuppressionwere noted as adverse events of special interest.

Gilteritinib is a potent type I inhibitor of both *FLT3* ITD and TKD, AXL (which has been implicated in leukemogenesis), and c-KIT at higher doses (potentially contributing to myelosuppression) [10]. Gilteritinib is also dosed once-daily with a prolonged half-life of over 130 h. FLT3 kinase inhibition mediated by gilteritinib has been shown to be dose-dependent [11] and sustained for several days after treatment [12]. In the phase 3 ADMIRAL trial [13], adults with first relapsed or refractory *FLT3* mutant AML (characterized by *FLT3* ITD and/or *FLT3* TKD) were randomized to receive either gilteritinib 120 mg/day or salvage chemotherapy and were allowed to proceed onto hematopoietic stem cell transplant similar to the QUANTUM-R trial. Gilteritinib resulted in statistically significant improvement in median OS over salvage chemotherapy (9.3 months vs 5.6 months, respectively, $P = .0007$). Furthermore, 37% of patients on the gilteritinib arm achieved overall responses, as compared with only 17% on the salvage chemotherapy arm. Giltertinib has also been evaluated in the upfront AML setting. In a phase 1 trial of gilteritinib plus 7 + 3 (including both dose-escalation and dose-expansion arms) [14], the combination was well-tolerated by 33 evaluable de novo *FLT3* mutant AML patients with dosing adjusted to consist of a 14-day regimen of gilteritinib 120 mg/day. Reported composite complete remission rate was 93.9%. Early results suggested that these patients experienced a median duration of remission of 14 months, while median OS was not reached at the time of presentation.

Midostaurin is a first-generation broad-spectrum tyrosine kinase inhibitor originally developed for its ability to inhibit various tyrosine kinases important in solid tumor biology. Midostaurin was the first FLT3 inhibitor approved for AML therapy, specifically in the frontline setting in combination with 7 + 3 chemotherapy for adult patients with newly diagnosed *FLT3* mutant AML. In the phase 3 RATIFY trial, over 700 newly diagnosed AML patients with *FLT3* mutations (TKD and/or ITD) were randomized to standard chemotherapy plus midostaurin or placebo with allogeneic transplantation allowed [15]. Those in the midostaurin arm had significantly prolonged OS and improved event-free survival (EFS), with benefit still statistically significant when censored for transplant.

Crenolanib is a newer generation highly potent type II *FLT3* TKI developed specifically for its ability to potently inhibit TKD and ITD mutations, as well as CSF1R and PDGFR [16]. Similar to gilteritinib, this type II inhibitor is effective against numerous known D835 mutations in the *FLT3* TKD that confer resistance to other FLT3 TKI therapies such as quizartinib and sorafenib [17,18]. In a small phase 2 trial [19], 29 de novo *FLT3* mutant AML patients received upfront 7 + 3 chemotherapy with crenolanib for induction and consolidation therapy followed by stem cell transplant or maintenance crenolanib therapy. High overall response rates of 83% after induction therapy were reported. Of 16 patients who had minimal residual disease (MRD) assays completed, 15 (93%) had MRD-negative disease at first complete remission. Furthermore, 2-year OS remains > 70% with a very low risk of relapse after the first year and similar long-term outcomes in patients proceeding onto consolidation and maintenance as compared with transplant.

To date, the outcomes of second-generation FLT3 TKIs combined with 7 + 3 in non-randomized trials have consistently yielded significantly higher complete remission (CR) and complete remission with incomplete count recovery (CRri) rates than seen following midostaurin combined with 7 + 3 by at least 20%–30% (Table 2) [14,15,19,20]. Further follow-up is needed to confirm the possibility of significantly enhanced median OS given the vast improvement in CR rates.

Unfit or older individuals with newly diagnosed AML (median age at presentation of 67 years) tend to have *FLT3*-negative disease, but *FLT3* mutation is more common in secondary AML. For patients with *FLT3* mutant AML who are not candidates for intensive

Table 2
Midostaurin and Second-generation TKIs in de novo younger and fit *FLT3*-mutant AML patients.

FLT3 TKI	No. pts	CR/CRi/CRh	2 yr OS	Ongoing
Midostaurin + 7 + 3 [15]	N = 717 (ph 3)	59%	60%	AraC/DNR vs. AraC/Ida
Quizartinib + 7 + 3 [20]	N = 16 (ph 1)	84%	Ph 3 ongoing	Phase 3 (7 + 3) ongoing
Crenolanib + 7 + 3 [19]	N = 38 (ph 2)	88%	79% Ph 3 ongoing	Phase 3 (mido) ongoing
Gilteritinib + 7 + 3 [14]	N = 30 (ph 1)	93%	Not known Ph 3 planned	Phase 3 (mido) planned

chemotherapy, FLT3 TKI are also actively being studied in combination with hypomethylating agents. In a phase 1 dose-finding study of gilteritinib and azacitidine, there were many durable responses maintained over multiple cycles of therapy [21]. The overall response rate was 67%, with some patients alive for more than a year from beginning treatment. In de novo patients who are *FLT3*-mutant , first- and second-generation FLT3 inhibitors have exhibited excellent tolerability and significant response rates when used in combination with hypomethylating agents (azacitidine or decitabine). Midostaurin and azacitidine yielded an overall response rate of 26%; sorafenib and azacitidine had an overall response rate of 46%; sorafenib and decitabine had an overall response rate of 83% (but was only tested in 6 patients), and gilteritinib and azacitidine had an overall response rate of 60% [22–24].

FLT3 TKIs are also increasingly being employed as maintenance therapy following allogeneic stem cell transplant to reduce the risk of *FLT3* mutant disease relapse. In two randomized phase 2 trials, patients receiving sorafenib had statistically significantly improved relapse-free survival ($P = .013$) and overall survival (OS) ($P = .03$) as well as lower nonrelapse mortality ($P = .011$) [25], than those not taking sorafenib. Midostaurin also produced a 46% relative reduction in relapse when compared to standard of care alone [26]. An ongoing large international phase 3 trial (BMT CTN 1506) randomizing patients with *FLT3* mutant disease to receive placebo vs gilteritinib maintenance after transplant is ongoing. Of note, results of the ADMIRAL trial support the use of FLT3 TKIs in the post-hematopoietic stem cell transplant setting for relapsed/refractory patients. Those who resumed gilteritinib in maintenance posttransplant had a median OS of 16.2 months as compared with 8.4 months for those who stopped gilteritinib therapy after transplant.

Best FLT3 inhibitor is context-dependent

Which is the best FLT3 inhibitor? I would argue that the best FLT3 inhibitor depends on the clinical setting in which it is being used. Currently midostaurin in combination with 7 + 3 is the standard of care for de novo *FLT3*-mutant AML; however, based on higher response rates, second-generation TKIs are likely to supplant midostaurin as the best inhibitor to use in this patient population. In posttransplant patients, sorafenib maintenance appears to improve outcomes by reducing relapse. Whether a second-generation TKI will supplant sorafenib remains to be seen. For *FLT3*-mutant patients unfit for intensive chemotherapy, second-generation TKIs together with hypomethylating agents or in novel combinations will probably improve upon the results of sorafenib and hypomethylating agents or non-FLT3 TKI-containing regimens. In the relapsed/refractory setting, while gilteritinib and quizartinib are welcome additions to the armamentarium, novel TKI combinations incorporating FLT3 inhibitors into treatment regimens together with conventional chemotherapy and/or other biological agents are needed to combat the current short OS times achieved with FLT3 TKI monotherapy.

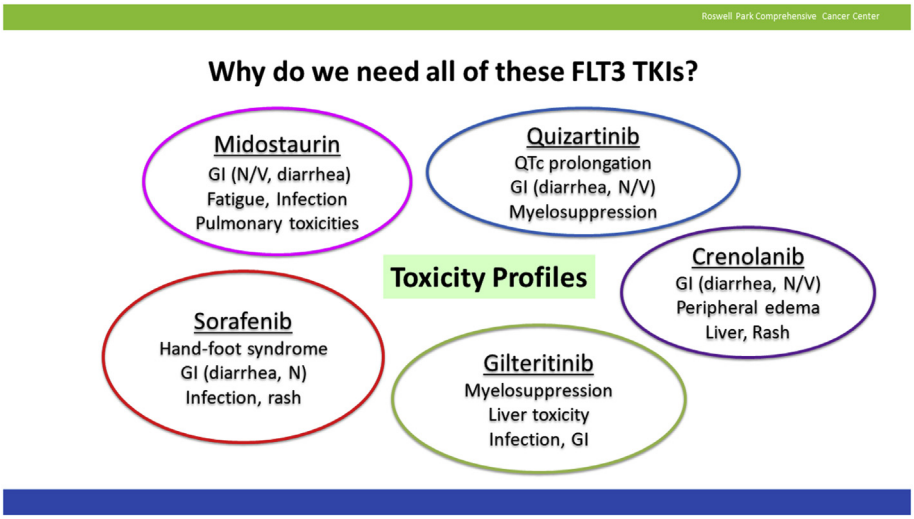

Fig. 1. Toxicity profiles of the different FLT3 TKIs.

Why do we need all these FLT3 inhibitors? Similar to BCR-ABL inhibitors for chronic myeloid leukemia, each FLT3 TKI exhibits a different toxicity profile (Fig. 1). In practice, individual patients with different comorbidities or who take other medications that may interact with some TKIs need a multitude of therapeutic options. The availability of 5 different TKIs will advance the field, and because each patient is different, there is no winner-takes-all.

The future of FLT3 inhibitors lies in several novel kinase inhibitors with target FLT3 as well as other mutant kinases in clinical development [7]. Ponatinib is a multikinase inhibitor with activity against *FLT3*-mutants including ITD and ITD691L but not D835, which is currently being used off label for AML patients. SEL24/MEN1703 is a PIM/FLT3 inhibitor with activity against multiple *FLT3*-mutants (ITD, ITD-691L, and D835) that is currently in phase 1 trial evaluation. FF-10101-01 is a unique irreversible FLT3 inhibitor with activity against ITD, ITD-691L, and D835 also in a phase 1 trial. Finally, MAX-40279 is an FGFR/FLT3 inhibitor against *FLT3* ITD and D835 being actively investigated in China. Of note, some of these broader-spectrum multikinase inhibitors appear to overcome *FLT3* mutations conferring resistance to more specific FLT3 TKIs.

Recently approved non-FLT3 targeted drug regimens for AML have also demonstrated significant efficacy in *FLT3*-mutant AML. For instance, the combination of azacitidine and venetoclax was reported to result in a 73% response rate as upfront treatment in a small number of *FLT3*-mutant AML patients [27]. Gemtuzumab ozogamicin plus 7 + 3 also conferred a statistically significant survival advantage in newly diagnosed *FLT3*-mutant AML patients. Of note, *FLT3*-mutant AML cells have been reported to have high expression of surface CD33 [28]. Whether these responses can be further improved by combining these regimens with FLT3 TKIs remain to be investigated.

Conclusion

Over the last several decades, the introduction of novel agents has transformed leukemia therapy for acute promyelocytic leukemia and chronic myeloid leukemia (BCR-ABL inhibitors for Philadelphia-chromosome-positive disease [29,30] into therapeutic success stories. These two diseases originally considered the most lethal of leukemias are now considered highly treatable due to arsenic and all-trans retinoic acid and BCR-ABL inhibitors, respectively. The addition of FLT3 TKIs to AML regimens holds similar promise to potentially transform *FLT3* mutant AML disease into a favorable subtype in the near future.

Disclosures

Consulting fees: Pfizer, Amgen, Agios, Celyad; Speakers bureau: Novartis, Jazz, Astellas; Contracted research: PI on clinical trials funded by Stemline, Eisai, Astellas, Amgen, Agios, Incyte, Forma, Tolero, Arog, Pfizer, Immunogen, Trovagene, Daiichi, Ono.

References

[1] Fröhling S, Schlenk RF, Breitruck J, Benner A, Kreitmeier S, Tobis K, et al. Acute myeloid leukemia. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood 2002;100:4372–80.
[2] Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 2016;374:2209–21.
[3] Pratz KW, Sato T, Murphy KM, Stine A, Rajkhowa T, Levis M. FLT3-mutant allelic burden and clinical status are predictive of response to FLT3 inhibitors in AML. Blood 2010;115:1425–32.
[4] Zarrinkar PP, Gunawardane RN, Cramer MD, Gardner MF, Brigham D, Belli B, et al. AC220 is a uniquely potent and selective inhibitor of FLT3 for the treatment of acute myeloid leukemia (AML). Blood 2009;114:2984–92.
[5] Galanis A, Ma H, Rajkhowa T, Ramachandran A, Small D, Cortes J, et al. Crenolanib is a potent inhibitor of FLT3 with activity against resistance-conferring point mutants. Blood 2014;123:94–100.
[6] Levis MJ, Perl AE, Altman JK, Cortes JE, Ritchie EK, Larson RA, et al. Results of a first-in-human, phase I/II trial of ASP2215, a selective, potent inhibitor of FLT3/Axl in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML). J Clin Oncol 2015;33. 15_suppl, 7003-7003.
[7] Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia 2019;33:299–312.
[8] Levis M. Quizartinib for the treatment of FLT3/ITD acute myeloid leukemia. Future Oncol 2014;10:1571–9.
[9] Cortes JE, Khaled SK, Martinelli G, Perl AE, Ganguly S, Russell NH, et al. Efficacy and safety of single-agent quizartinib (Q), a potent and selective FLT3 inhibitor (FLT3i), in patients (pts) with FLT3-internal tandem duplication (FLT3-ITD)-mutated relapsed/refractory (R/R) acute myeloid leukemia (AML) enrolled in the global, phase 3, randomized controlled Quantum-R Trial. Blood 2018;132:563. abstr.
[10] Mori M, Kaneko N, Ueno Y, Yamada M, Tanaka R, Saito R, Shimada I, et al. Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. Investig New Drugs 2017;35:556–65.
[11] Perl AE, Altman JK, Cortes J, Smith C, Litzow M, Baer MR, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. Lancet Oncol 2017;18:1061–75.
[12] Lee LY, Hernandez D, Rajkhowa T, Smith SC, Raman JR, Nguyen B, et al. Preclinical studies of gilteritinib, a next-generation FLT3 inhibitor. Blood 2017;129:257–60.
[13] Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Stefania Paolini S, et al. Gilteritinib significantly prolongs overall survival in patients with FLT3-mutated (FLT3mut+) relapsed/refractory (R/R) acute myeloid leukemia (AML): results from the phase III ADMIRAL trial. On: Proceedings of the 110th Annual Meeting of the American Association for Cancer Research; 2019 March 29-April 3; Atlanta, GA. Philadelphia (PA): AACR; 2019. Abstract CT184.
[14] Pratz KW, Cherry Mohamad, Jessica K, Altman, Cooper Brenda, Cruz Jose Carlos, Jurcic Joseph G, et al. Updated results from a phase 1 study of gilteritinib in combination with induction and consolidation chemotherapy in subjects with newly diagnosed acute myeloid leukemia (AML). Blood 2018;132:564. abstr.
[15] Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017;377:454–64.
[16] Galanis A, Rajkhowa T, Muralidhara C, Ramachandran A, Levis M. Crenolanib: a next generation FLT3 inhibitor. Cancer Res 2014;72:3660. (8 Supplement):abstr.
[17] Smith CC, Lin K, Stecula A, Sali A, Shah NP. FLT3 D835 mutations confer differential resistance to type II FLT3 inhibitors. Leukemia 2015;29:2390–2.
[18] Tarlock K, Hylkema TA, Pollard JA, Hansen ME, Ries R, Sweat R, et al. Functional assessment of novel diagnostic FLT3 mutations and inhibition by kinase inhibitors. EHA Learning Center. EHA Annual Meeting Jun 2017;23:181471. abstr P184.
[19] Wang ES, Tallman MS, Stone RM, Walter RB, Karanes C, Jain V, et al. Low relapse rate in younger patients ≤ 60 years old with newly diagnosed FLT3-mutated

acute myeloid leukemia (AML) treated with crenolanib and cytarabine/anthracycline chemotherapy. Blood 2017;130:566. abstr.
[20] Altman JK, Foran JM, Pratz KW, Trone D, Cortes JE, Tallman MS. Phase 1 study of quizartinib in combination with induction and consolidation chemotherapy in patients with newly diagnosed acute myeloid leukemia. Am J Hematol 2018;93(2):213–21.
[21] Esteve J, Schots R, Del Castillo TB, Lee JH, Wang ES, Dinner S, et al. Multicenter, open-label, 3-arm study of gilteritinib, gilteritinib plus azacitidine, or azacitidine alone in newly diagnosed FLT3 mutated (FLT3mut+) acute myeloid leukemia (AML) patients ineligible for intensive induction chemotherapy: findings from the safety cohort. Blood 2018;132:2736. abstr.
[22] Cooper BW, Kindwall-Keller TL, Craig MD, Creger RJ, Hamadani M, Tse WW, et al. A phase I study of midostaurin and azacitidine in relapsed and elderly AML patients. Clin Lymphoma, Myeloma & Leukemia 2015;15(7):428–432 e2.
[23] Ravandi F, Alattar ML, Grunwald MR, Rudek MA, Rajkhowa T, Richie MA, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood 2013;121(23):4655–62.
[24] Muppidi MR, Portwood S, Griffiths EA, Thompson JE, Ford LA, Freyer CW, et al. Decitabine and sorafenib therapy in FLT-3 ITD-mutant acute myeloid leukemia. Clin Lymphoma, Myeloma & Leukemia 2015;15(Suppl):S73–9.
[25] Burchert A, Bug G, Finke J, Stelljes M, Rollig C, Wäsch R, et al. Sorafenib as maintenance therapy post allogeneic stem cell transplantation for FLT3-ITD positive AML: results from the randomized, double-blind, placebo-controlled multicentre Sormain trial. Blood 2018;132:661. abstr.
[26] Maziarz RT, Patnaik MM, Scott BL, Mohan SR, Abhinav Deol A, Scott D, Rowley SD, et al. Radius: a phase 2 randomized trial investigating standard of care ± midostaurin after allogeneic stem cell transplant in FLT3-ITD-mutated AML. Blood 2018;132:662. abstr.
[27] Pollyea DA, Pratz Keith W, Jonas Brian A, Anthony Letai, Pullarkat Vinod A, Wei Andrew, et al. Venetoclax in combination with hypomethylating agents induces rapid, deep, and durable responses in patients with AML ineligible for intensive therapy. Blood 2018;132:285. abstr.
[28] Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012;379:1508–16.
[29] Chen SJ, Zhou GB, Zhang XW, Mao JH, de Thé H, Chen Z. From an old remedy to a magic bullet: molecular mechanisms underlying the therapeutic effects of arsenic in fighting leukemia. Blood 2011;117:6425–37.
[30] Mughal TI, Radich JP, Deininger MW, Apperley JF, Hughes TP, Harrison CJ, et al. Chronic myeloid leukemia: reminiscences and dreams. Haematologica 2016;101:541–58.