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General AML

ISAL 2019 | Therapeutic advances for patients with acute myeloid leukemia

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At the Acute Leukemias XVII Biology and Treatment Strategies biennial international symposium in Munich, Germany, the latest developments in targeted therapies to improve outcomes in patients with acute myeloid leukemia (AML) was widely discussed amongst experts.

Major advances have been made in the treatment of patients with *fms-like tyrosine kinase 3*-internal tandem repeat (FLT3-ITD) AML. In 2017 Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved the multi-targeted tyrosine kinase inhibitor, midostaurin, which has shown clinical efficacy in patients with *FLT3*-ITD AML.[1] On 25 February 2019, Professor Richard Stone, from the Dana-Farber Cancer Institute, Boston, US, presented a talk discussing the evolution of the first generation FLT3 inhibitor, midostaurin, including findings from the RATIFY study.[2] Results from the RATIFY trial (NCT00651261), in which patients with newly diagnosed FLT3 mutated AML received standard chemotherapy plus midostaurin or placebo, showed a 23% reduced risk of death in patients receiving midostaurin compared to placebo. Median overall survival (OS) in the midostaurin group was significantly longer than the placebo group (74.7 months [95% CI, 31.7–not reached] *vs* 25.6 months [95% CI, 18.6–42.9], *P* = 0.009).[3] Professor Stone outlined that further investigations are required to better understand scheduling, and differences between patient subgroups. Moreover, the RADIUS study assessed midostaurin in combination with standard-of-care (SOC) therapy *vs* SOC alone, in patients with FLT3-ITD mutant AML following allogeneic stem cell transplantation (alloSCT). Professor Stone outlined that results from the RADIUS trial demonstrated a reduced predicted risk of relapse at 18 months following alloSCT by 54% in the midostaurin plus SOC *vs* SOC alone group.[4] Professor Stone concluded the development of midostaurin had been challenging, involving the work of a significant number of groups, who have aided in the approvals of midostaurin.

The development of FLT3 inhibitors have provided improvements to outcomes in patients with FLT3 mutant AML, with work in targeted therapies focused on providing improved on-target efficacy, and off-target toxicity. To this effect, Associate Professor Mark Levis, from Johns Hopkins University, Baltimore, US, discussed the development and clinical efficacy of second generation FLT3 inhibitors quizartinib and gilteritinib. In the previously reported QuANTUM-R trial (NCT02039726), the oral, selective FLT3 inhibitor, quizartinib, was shown to improve median OS in patients with FLT3 mutant relapsed/refractory (R/R) AML, compared to salvage chemotherapy (6.2 months [95% CI, 5.3–7.2] *vs* 4.7 months [95% CI, 4.0–5.5], HR = 0.76 [95% CI, 0.58–0.98], *P* = 0.0177).[5,6] Furthermore, the oral and selective FLT3/AXL inhibitor, gilteritinib, showed clinical efficacy in an interim analysis with a complete remission/complete remission with partial hematologic recovery (CR/CRh) rate of 21% for gilteritinib (ADMIRAL study, NCT02421939).[7] Results from this trial have led to the FDA approval in 2018 and the EMA regulatory review in 2019 for gilteritinib. Associate Professor Levis concluded that with gilteritinib and quizartinib moving into routine clinical use, the development of the oral FLT3 inhibitor crenolanib is promising but requires further testing. Moreover, gilteritinib was shown to be well-tolerated and an effective single-agent therapeutic in patients with R/R AML, with its lower potency providing potential benefits in terms of safety. On the other hand, quizartinib has a high potency providing efficacy early in the therapeutic pathway, however, myelosuppression can be a challenge in some patients.

Professor Jeffrey Lancet, a member of our North-American Steering Committee, from the Moffitt Cancer Center & Research Institute, Tampa, US, discussed the latest innovations in conventional chemotherapy for patients with AML.[8] The optimization of drug delivery has been modest over recent years, with previous attempts to introduce dose intensification with anthracyclines, multidrug modulation, and liposomal drug administration. Professor Lancet highlighted that the bilamellar liposome formulation of daunorubicin and cytarabine, known as CPX-351, was associated with significantly improved OS rates compared to the conventional '7+3' chemotherapeutic regimen in patients with newly diagnosed secondary AML (9.56 months *vs* 5.96 months, HR = 0.69 [95% CI, 0.52–0.90], *P* = 0.003).[9] In addition to this, the safety profile between treatment arms was comparable, demonstrating the safety of the liposomal CPX-351 delivery system. Professor Lancet concluded that the nanoscale liposomal delivery system, demonstrated by CPX-351, has shown to be an effective new therapeutic strategy to deliver chemotherapy in patients with secondary AML.

In conclusion, the discussions at the Acute Leukemias XVII Biology and Treatment Strategies biennial symposium demonstrated that the field of novel therapies for AML is rapidly developing, providing improved treatment options and a greater treatment repertoire for patients with AML.

References

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