FLT3, General AML

ASCO 2018 | New agents in AML

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At the 2018 American Society of Hematology Annual Meeting, the AML Global Portal (AGP) attended a poster discussion session. At this session, Alice Mims, The Ohio State University, Columbus, US, discussed new novel agents in acute myeloid leukemia (AML).

The standard cytarabine and anthracyclines through the “3 + 7 regimen” have been the mainstay treatment for AML. The speaker highlighted that times are really changing for AML: “a few years ago, initial treatment decisions were based on age, performance status and co-morbidities”. Data from cytogenetics and molecular mutations usually return after patients had started therapy and would be used to decide whether to perform allogeneic transplantation or consolidative regimens. For patients who were not candidates, a lower intensity treatment is administered or if necessary they receive supportive care in hospice. In 2017, four new drugs including midostaurin (for newly diagnosed \textit{FLT3}-mutated AML patients), enasidenib (for \textit{IDH2}-mutated relapsed/refractory AML patients), CPX-351 (therapy-related AML, or AML with MDS-related changes) and gemtuzumab ozogamicin (GO) have been approved by the US Food and Drug Administration (FDA), and several more ongoing studies will support new promising treatments for AML.

The speaker then discussed three abstracts (#7017, #7019 and #7020) presented at the ASCO hematology poster session.

\textbf{Abstract 7017: Post hoc exploratory analysis of two phase 2 trials of quizartinib monotherapy in patients (pts) with \textit{FLT3}-ITD–mutated (mu) relapsed/refractory (R/R) AML with or without prior 1st-generation \textit{FLT3} tyrosine kinase inhibitors (TKI) treatment}

Quizartinib is a highly potent second-generation \textit{FLT3} inhibitor with strong clinical anti-leukemic activity in patients with \textit{FLT3}-ITD mutated R/R AML. In order to assess quizartinib activity in patients with prior \textit{FLT3} tyrosine kinase inhibition therapy, Mark J. Levis, Johns Hopkins University, Baltimore, MD, and colleagues performed a post-hoc exploratory analysis on two phase II studies (NCT01565668 [study A] & NCT00989261 [study B]), which both evaluated quizartinib monotherapy in \textit{FLT3} mutated R/R AML patients.

Of the 261 \textit{FLT3}-ITD mutated patients enrolled in study A, 27 patients had prior therapy with sorafenib or midostaurin. Composite complete remission (CRc) and overall response rates (ORR) with quizartinib were 33% (9/27) and 67% (18/27), respectively, in prior-TKI-treated patients, compared with 53% (117/221) and 75% (165/221), respectively, in the TKI-naive patients.

Of the 72 patients enrolled in study B, 11 patients had received prior TKIs. CRc and ORR were 36% (4/11) and 45% (5/11), respectively, in prior-TKI-treated pts, compared with 48% (29/61) and 69% (42/61), respectively, in the TKI-naive patients. Six of these patients in this post-hoc analysis were bridged to allogeneic transplantation.

Alice Mims concluded that the findings of this study suggest that “quizartinib may be a reasonable method to try to allow for a few months of disease control, or as a potential bridge to transplantation in patients with prior \textit{FLT3} inhibitor exposure”
Abstract 7019: First-in-human study of ABBV-075 (mivebresib), a pan-inhibitor of bromodomain and extra terminal (BET) proteins, in patients (pts) with relapsed/refractory (RR) acute myeloid leukemia (AML): Preliminary data.

Dr. Mims then discussed a new target in AML, bromodomain and extraterminal domain (BET) proteins. BET proteins are epigenetic readers and function by binding acetylated lysines on histones to recruit the mediator complex and other proteins to chromatin. In AML, BET proteins are upregulated and this can lead to abnormal transcriptional programs.

The speaker then discussed a study by Gautam Borthakur from the MD Anderson Cancer Center, Houston, TX. Borthakur et al. reported preliminary data from an ongoing phase I, first-in-human, dose escalation study (NCT02391480) of ABBV-075, a BET inhibitor, in patients with R/R AML. The recommended phase 2 dose was determined in patients with solid tumors.

In this study, 23 R/R AML patients were first treated with monotherapy (n = 12) and if there was no response, they went on to receive combination with venetoclax (n = 11). At present, there has been no report of any dose-limiting toxicities. Most common grade 3–4 treatment-emergent adverse events include anemia (52%), thrombocytopenia (44%) and febrile neutropenia (26%). The ORR for evaluable patients was 17.6% (3/17).

In summary, "ABBV-075 was well tolerated and showed antileukemic effects in patients with R/R AML".

Abstract 7020: Analysis of anti-leukemic activity, predictive biomarker candidates, immune activation and pharmakodynamics in R/R AML and MDS in response to treatment with bemcentinib (BGB324), a first-in class selective AXL inhibitor, in a phase II open-label, multi-centre study.

Dr. Mims then described another target in AML, AXL. AXL overexpression has been reported to be an independent negative prognostic factor in AML. Bjorn T. Gjertsen and colleagues reported data from a phase I/II study of bemcentinib (BGB324), a first-in-class, oral selective inhibitor of AXL, in 32 patients with R/R AML or MDS.

The maximum tolerated dose for BGB324 was 200 mg orally daily. Three patients achieved CR (AML [n = 1], MDS [n = 2]) with AML and three patients had partial remissions (AML [n = 2], MDS [n = 1]). Additionally, pretreatment soluble AXL levels appear to be decreased in responders versus non-responders. "Soluble AXL levels may be a predictive biomarker for AXL inhibition", however further investigations are required Dr. Mims noted.

In conclusion, Dr. Mims highlighted that both BET and AXL inhibition appeared to be new and exciting targets in myeloid malignancies. Identifying response predictors to these novel agents would be crucial.

References