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General AML, FLT3

Is there a clinical benefit for lestaurtinib in previously untreated AML patients?

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Dr Steven Knapper from the Cardiff University of Medicine, Cardiff, and colleagues recently published data from the AML15 (ISRCTN17161961) and AML17 (ISRCTN55675535) trials. The data were published on the 21st of November 2016 in Blood. In these studies, lestaurtinib, a FLT3 inhibitor, was added to front line chemotherapy in patients with previously untreated Acute Myeloid Leukemia (AML) in order to investigate its effect on clinical outcome of patients. The primary endpoints of this study were Overall Survival (OS) and Relapse Free Survival (RFS).

Highlights:

- 500 patients (median age = 49) with FLT3 mutations were enrolled
- FLT3 ITD mutations = 74%; FLT3 TKD = 23%; both mutations = 2%
- Patients received 4 cycles of chemotherapy with or without oral lestaurtinib
- No significant difference in 5-year OS between control & lestaurtinib; 45% *vs* 46%, HR = 0.90, *P* = 0.3
- No significant difference in 5-year RFS between control & lestaurtinib; 36% *vs* 40%, HR = 0.88, *P* = 0.3
- Azole therapy in patients receiving lestaurtinib significantly improves survival; HR = 0.57, *P* = 0.02
- Post relapse, patients receiving gemtuzumab ozogamicin had significantly better survival; HR = 0.49, *P* = 0.04

The authors concluded that lestaurtinib in combination with first line chemotherapy in previously untreated AML patients did not have an overall clinical benefit, however, it was feasible. Additionally, patients with sustained FLT3 inhibitory activity had an improved OS and lower rates of relapse.

Abstract

The clinical benefit of adding FLT3-directed small molecule therapy to standard first-line treatment of acute myeloid leukemia (AML) has not yet been established. As part of the UK AML15 and 17 trials, patients with previously-untreated AML and confirmed FLT3-activating mutations, mostly aged <60 years, were randomised to receive oral Lestaurtinib (CEP701), or not, following each of four cycles of induction and consolidation chemotherapy. Lestaurtinib was commenced 2 days after completing chemotherapy and administered in cycles of up to 28 days. The trials ran consecutively; primary endpoints were overall survival in AML15 and relapse-free survival in AML17; outcome data were meta-analysed. 500 patients were randomised between Lestaurtinib and control; 74% had *FLT3*-ITD mutations, 23% *FLT3*-TKD point mutations, 2% both types. No significant differences were seen in either 5-year overall survival (Lestaurtinib 46% vs control 45%, HR 0.90 [0.70-1.15], p=0.3) or 5-year relapse-free survival (40% vs 36%, HR 0.88 [0.69-1.12], p=0.3). Exploratory sub-group analysis suggested survival benefit with Lestaurtinib in patients receiving concomitant azole anti-fungal prophylaxis and gemtuzumab ozogamicin with the first course of chemotherapy. Correlative studies included analysis of in vivo FLT3 inhibition by plasma inhibitory activity assay and indicated improved overall survival and

significantly reduced rates of relapse in Lestaurtinib-treated patients who achieved sustained >85% FLT3 inhibition. In conclusion, combining Lestaurtinib with intensive chemotherapy proved feasible in younger patients with newly-diagnosed *FLT3*-mutated AML but yielded no overall clinical benefit. The improved clinical outcomes seen in patients achieving sustained FLT3 inhibition encourage continued evaluation of FLT3-directed therapy alongside front-line AML treatment. The UK AML15 and AML17 trials are registered at www.isrctn.com/ISRCTN17161961 and www.isrctn.com/ISRCTN55675535 respectively.

References

1. Knapper. S. *et al.* A randomised assessment of adding the kinase inhibitor lestaurtinib to 1st-line chemotherapy for FLT3-mutated AML. Blood. 2016 Nov 21; DOI: 10.1182/blood-2016-07-730648 [Epub ahead of print].