The Efficacy of the FLT3 Inhibitor Lestaurtinib in AML Depends on Adequate Plasma Inhibitory Activity (PIA), and Is Unaffected by Rising FLT Ligand Levels: An Update of the NCRI AML15 & 17 Trials

The receptor tyrosine kinase FLT3 remains the subject of intense clinical interest as a therapeutic target in AML. FLT3-activating mutations are seen in one-third of adults at diagnosis and are associated with adverse prognosis. The multi-targeted kinase inhibitor lestaurtinib (CEP701) has potent activity against FLT3. In monotherapy studies, sustained plasma drug activity sufficient to inhibit FLT3 by >85% was found to be a prerequisite for clinical response (1,2). A recently-reported randomized study of lestaurtinib combined with chemotherapy in relapsed FLT3-mutated AML failed to demonstrate improved clinical outcome with lestaurtinib, but definitive conclusions were limited by the relatively low rate (58%) of patients achieving >85% FLT3 inhibition (3). In that study, rising levels of FLT3 ligand (FL) were noted during chemotherapy; raised FL levels have been reported to impede the in vitro efficacy of FLT3 inhibitors (4).

As part of an ongoing randomised assessment (NCRI AML15 and 17 Trials) 118 newly-diagnosed FLT3-mutated non-APL AML patients (median age 49 [range 16-66], 86 ITD, 30 TKD point mutation, 2 both FLT3 mutations, 87% intermediate risk karyotype) received lestaurtinib for up to 28 days following each of 4 courses of chemotherapy. Based on early pharmacokinetic data, starting dose of lestaurtinib was adjusted according to concomitant anti-fungal drug use: 40mg bid in azole treated patients, 80mg bid in other patients. Patients received a median 3 courses of lestaurtinib (range 0-4); no excess severe adverse events have been reported in lestaurtinib-treated patients. Median follow-up is now 30 months (range 9-47). 49 patients underwent allogeneic SCT (37 in 1st CR, 28 myeloablative conditioning, 21 RIC). In a non-randomised comparison of clinical outcome with a matched historical age-matched control population of 118 FLT3-mutated patients entering the AML15 Trial prior to the opening of the lestaurtinib randomisation, there was a modest improvement in complete remission (CR/CRi) rate (92% vs 90% historical control), 2-year cumulative relapse rate (47% vs 55%) and 2-year overall survival (50% vs 47%).

Trough FLT3 plasma inhibitory activity (PIA) was measured on day 14 of each lestaurtinib course. 169 timepoints were assessed in 84 patients with 88% of patients achieving at least 1 FLT3 PIA measurement of >85%. FLT3 PIA of >85% was seen at 75% of individual timepoints (127/169). Rates of relapse were significantly lower in patients that achieved FLT3 PIA>85% at all evaluated timepoints: the 2-year relapse rate was 38% in inhibited vs 61% in non-inhibited patients (22/58 vs 16/26) (p=0.01) where results were available for 1 or more timepoints, 23 vs 58% (6/28 vs 10/18)(p=0.01) for 2 or more timepoints and 15% vs 64% (2/14 vs 7/11)(p=0.007) for 3 or more timepoints. Significantly increased 2-year overall survival was seen in patients that achieved >85% PIA at 1 or more timepoints, 64% in inhibited vs 40% in non-inhibited patients (37/58 vs 10/26)(p=0.01).
Mean day 14 FL concentrations rose through successive courses of lestaurtinib treatment from 529 pg/ml during course 1 to 1350 pg/ml, 2575 pg/ml and 2467 pg/ml respectively during courses 2, 3 and 4. No increase was seen in alpha-1-acid glycoprotein levels. Despite rising FL levels, no fall off was seen in achievement of FLT3 inhibition: day 14 FLT3 PIA>85% was achieved by 75% of assayed patients during course 1 (51/68), 80% during course 2 (39/49), 78% during course 3 (25/32) and 60% during course 4 (12/20). No difference was seen in FLT3 PIA between patients grouped according to high or low FL concentration.

These data provide evidence of an emerging relationship between sustained FLT3 inhibition and improved clinical outcome when tyrosine kinase inhibition is combined with standard chemotherapy in newly diagnosed AML. Rising FL levels through successive courses of therapy failed to impede target inhibition. The sequential combination of lestaurtinib with chemotherapy continues to be evaluated in the ongoing randomized NCRI AML17 Trial.