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FLT3

FLT3 ligand as a biomarker for AML

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During the 1st NCRI AML academy meeting, Professor Matthew Collin from Newcastle University, Newcastle upon Tyne, UK, presented the potential utility of Fms-like tyrosine kinase 3 ligand (FLT3L) measurement in *FLT3*-positive acute myeloid leukemia (AML) for the early assessment of response and monitoring of remission status.[1] Presently, the standard of care is expectant and remission is formally assessed by examination of the bone marrow following hematopoietic recovery. Patients will not know that they have resistant or refractory disease until several weeks after completing the first course of chemotherapy, a problem that is frequently compounded by delayed blood count recovery in those most at risk of treatment failure.

Serum FLT3L as a biomarker of progenitor cell mass and prognosis in AML[1,2]

Methods

- Single-center patients/controls
  - Cohort A: Patients with heterozygous mutation of *GATA2,* aplastic anemia, MDS and AML were recruited from the Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK
  - Cohort B: 84 patients were recruited at Newcastle, UK and eight patients at Johns Hopkins, Baltimore, US
  - All but two patients received intensive induction chemotherapy with cytarabine in combination with either daunorubicin, etoposide or mitoxantrone
- UK NCRI AML 17 study patients
  - Newly diagnosed patients with AML or high-risk MDS (≥ 10% marrow blasts)
  - 325 patients with *FLT3* mutation
  - 140/325 provided a blood sample at Day 26 for measurement of FLT3L

Results

The relationship between FLT3L level and progenitor cell mass was explored in patients from Cohort A:

- Measurement of FLT3L by ELISA revealed that *FLT3*-positive AML was associated with depletion of FLT3L to low or undetectable levels (limit of detection 7pg/mL)
- Patients with heterozygous mutation of *GATA2* and aplastic anemia had highly elevated serum FLT3L
- Patients with MDS exhibited an increased variance of FLT3L levels
- Association of FLT3L with remission assessment post-chemotherapy

After induction chemotherapy, FLT3L was restored in patients achieving a complete response (CR), but remained depressed in patients with refractory disease:

- Samples from 28 patients with undetectable FLT3L at diagnosis in Cohort A were available after two rounds of intensive chemotherapy at the time of remission assessment (28–42 days after the start of each round of chemotherapy)
- Fifteen patients were in morphological CR after both courses of chemotherapy and showed recovery of FLT3L to normal or supra-normal levels at both time points
- Five patients who did not achieve morphological CR after the first course but subsequently entered remission after the second course also demonstrated increasing FLT3L over both cycles
- In contrast, FLT3L remained undetectable in five patients who did not enter CR after two cycles of chemotherapy
- Three patients thought to be in morphological CR after the first course failed to show any appreciable recovery of FLT3L after either course one or course two. These patients all relapsed within six months of diagnosis at 114-172 days, compared with relapse-free survival of 317–825 days for patients whose FLT3L was elevated after treatment

Weekly sampling was performed in 12 patients (four Cohort A and eight Cohort B) and revealed differences in the kinetics of FLT3L response during the first six weeks of treatment, proportionate to the clearance of blasts and cellularity of the BM:

- Six patients who achieved CR showed FLT3L elevation of 1000–4000 pg/mL, peaking between Day 14 and 21 and returning to the normal range after chemotherapy
- In contrast, four patients who did not achieve CR showed modest elevations of less than 1000 pg/mL that subsequently dropped back to below normal or undetectable levels at Day 42
- Two patients still had pancytopenia after chemotherapy induction and were found to have hypocellular bone marrow without detectable blasts. In these patients, FLT3L remained high (>1000pg/ml). One patient was salvaged by hematopoietic stem cell transplantation (HSCT) but the other died of sepsis without any count recovery

Analysis of the UK NCRI AML17 CR and survival data:

- FLT3L was measured at day 26 of induction, following 10 days of chemotherapy and 14 days of either TKI lestaurtinib or placebo
- Attainment of CR was associated with higher FLT3L at Day 26 ($P < 0.0001$)
- There was a significantly lower median level of FLT3L in patients not achieving a CR, including four patients with undetectable levels
    - None of the patients with undetectable FLT3L at Day 26 achieved a CR
- Day 26 FLT3L was also associated with survival
    - FLT3L $\leq$ 291pg/mL was associated with inferior EFS and FLT3L > 1185pg/mL was associated with higher overall survival (OS; $P = 0.0119$)
    - Of note, a subgroup of 20 patients with high FLT3L (> 1185pg/mL) achieved OS of > 80% at three years, compared with approximately 50% in the remainder of the cohort. The authors speculated that very high levels of FLT3L occur in association with deep remissions in chemo-sensitive disease and that further studies are required to validate these thresholds and determine their prognostic utility

Serial measurement of FLT3L in patients who received an HSCT also indicated at the potential prognostic value of declining FLT3L to identify relapse:

- Samples were collated from Day seven to 24 months from patients receiving HSCT in Cohort A
- Eight patients suffered a relapse and seven patients had continuing CR over the same period
- In all patients, FLT3L increased to a peak of approximately 1,000pg/ml during the aplastic phase, immediately following the conditioning
- FLT3L remained at or above physiological levels in seven patients with sustained remission, but declined and became undetectable in the eight patients who relapsed

Conclusions

- Measurement of FLT3L may provide an inexpensive, rapid and non-invasive means of assessing remission status in AML with the potential to inform clinical decisions
- In patients who receive an HSCT, post-transplant monitoring of FLT3L may provide insights into pancytopenia, distinguishing between poor graft function or myelosuppression and incipient relapse
- MRD testing will likely be specific to the intensity of treatment. For example, different response kinetics have been reported with lower intensity treatment with azacytidine and sorafenib, where FLT3L levels did not rise to the levels seen in prior studies of patients receiving cytotoxic chemotherapy[2,3]
- Prospective studies are required to validate the results

References

1. Collin M. Serum Flt3 ligand is an indicator of progenitor cell mass and prognosis in acute myeloid leukemia. Oral presentation. 2019 Sep 20. 1st NCRI AML academy meeting 2019.
2. Milen P, Wilhelm-Benartzi C, Grunwald M, *et al.,* Serum Flt3 ligand is biomarker of progenitor cell mass and prognosis in acute myeloid leukemia. bioRxiv 588319; DOI: https://doi.org/10.1101/588319
3. Ravandi F, Alattar ML, Grunwald, *et al.,* Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood. DOI: 2013;121:4655–62.