LymphomaHub

DLBCL, HL, PTCL, CTCL

Concentration and integrity of ccfDNA presents as a potentially useful non-invasive technique for diagnosis and prognosis of patients with Lymphoma

Terri Penfold | Aug 30, 2017

A report of a study by Mao Li from West China Hospital, Sichuan University, Sichuan, China, *et al.,* which aimed to determine if the concentration and integrity index of Circulating Cell-Free DNA (ccfDNA) in plasma could aid diagnosis and monitoring progression in patients with Lymphoma, was published by the Annals of Hematology as an Epub ahead of print on 16th June 2017.

Plasma samples were collected at the time of initial diagnosis from patients at West China Hospital of Sichuan University diagnosed from September 2014 to January 2016. Overall, plasma samples from 174 patients with Lymphoma and 80 healthy individuals were included in the study. The total concentration of ccfDNA was calculated using a fluorometry method and the DNA Integrity Index (DII; the ratio of longer to shorter DNA fragments) for the APP gene was detected using real-time quantitative PCR. DII would be 1.0 when the template DNA was not truncated and 0.0 when all of the template DNA was truncated into fragments smaller than 180 base pairs.

Key Highlights:

Patients:

- Lymphoma subtypes = B-NHL (n=126; DLBCL most common, n=98), HL (n=18), T-NHL (n=9), and extranodal NK/TCL (n=21)
- Median follow-up = 13.5 months (range, 1–36 months)

Concentration of ccfDNA:

- Median ccfDNA concentration in healthy individuals was 209.0ng/ml (mean, 222.5ng/ml; range, 100.0–456.0ng/ml) *vs* 0ng/ml (mean, 1,407.6ng/ml; range, 100.0–14,180ng/ml) for those with Lymphoma; $P < 0.0001$
- Median ccfDNA concentration by subtype:
  - HL = 681.0ng/ml; $P = 0.001$
  - DLBCL = 845.0ng/ml; $P < 0.0001$
  - Other types of B-NHL = 332.0ng/ml; $P < 0.0001$
  - T-NHL = 942.0ng/ml; $P < 0.0001$
  - NK/TCL = 662.0ng/ml; $P < 0.0001$
- Elevated levels of ccfDNA associated with an increased risk of Lymphoma; a 10.0ng/ml increase in ccfDNA concentration increased risk of Lymphoma by 7.3% (odds ratio, 1.073; 95% CI, 1.045–1.102)

Integrity of ccfDNA:

- Median DII for Lymphoma patients was 0.39 *vs* 21 for healthy individuals ($P < 0.0001$)
- Median DII values by subtype:
  - HL = 0.37; $P < 0.0001$)
  - DLBCL = 0.43; $P < 0.0001$)
  - Other types of B-NHL = 0.34; $P = 0.002$
  - T-NHL = 0.42; $P = 0.008$
  - NK/TCL = 0.33; $P = 0.001$

Correlation with clinicopathological features and prognostic significance of ccfDNA in DLBCL:

- Advanced stage disease (stage IIB–IV) and elevated LDH levels associated with increased ccfDNA levels and DII
- B-symptoms also correlated with increased ccfDNA concentration and DII
- Patients with adverse prognostic score had higher ccfDNA levels (significant among all Lymphoma patients and just those with DLBCL)
- Patients with ccfDNA concentration >1,586ng/ml had a 2-year PFS rate of 44% (95% CI, 15–73%) *vs* 78% (95% CI, 55–99%) in patients with ccfDNA concentration ≤1,586ng/ml ($P = 0.001$)
- Patients with a DII >0.61 had a 2-year PFS rate of 59% (95% CI, 38–79%) *vs* 87% (95% CI, 69–100%) in patients with a DII ≤61 ($P < 0.0001$)
- ccfDNA concentration and DII were associated with PFS in univariate analysis
- On multivariate analysis, DII was found to be a statistically independent prognostic factor (HR, 3.04; 95% CI, 1.197–7.696; $P = 0.019$)

This study demonstrated that at time of diagnosis, patients with Lymphoma compared to healthy individuals often have increased levels and longer strands of ccfDNA. Moreover, this correlated with clinical parameters and was shown to be a predictor of poor outcome in patients with DLBCL. The authors conclude that measuring the concentration and integrity of ccfDNA from Lymphoma patient plasma “might be a useful non-invasive technique for clinical practice.” Lastly, the group emphasize that future prospective studies with larger numbers of patients and longer follow-up should be conducted to evaluate ccfDNA analysis.

Abstract:

Circulating cell-free DNA (ccfDNA) has been shown to be associated with the clinical characteristics and prognosis of cancer patients. Our objective was to assess whether the concentration and integrity index of ccfDNA in plasma may be useful for diagnosing and monitoring the progression of patients with lymphoma. We included plasma samples from 174 lymphoma patients and 80 healthy individuals. The total concentration of ccfDNA was determined using a fluorometry method, and the DNA integrity index (DII), which is the ratio of longer to shorter DNA fragments, for the APP gene was detected using real-time quantitative PCR. The median levels of the ccfDNA concentration and the DII in patients with lymphoma were significantly higher than those in controls (both P < 0.0001). Increases in the ccfDNA concentration and the DII were associated with advanced stage disease, elevated lactate dehydrogenase levels, and a higher prognosis score.

In patients with diffuse large B cell lymphoma (DLBCL), high levels of ccfDNA (both concentration and the DII) showed an inferior 2-year progression-free survival (PFS) (P = 0.001; P < 0.0001, respectively). Our study provides quantitative and qualitative evidence in favor of using ccfDNA analysis in lymphoma patients for diagnostic and prognostic assessments.

References

1. Li M.*et al.* Assessment of the circulating cell-free DNA marker association with diagnosis and prognostic prediction in patients with lymphoma: a single-center experience. Annals of Hematology. 2017 Aug;96(8):1343-1351. DOI: 10.1007/s00277-017-3043-5. Epub 2017 Jun 16.