The clinical potential of circulating cell-free DNA (cfDNA) for real-time longitudinally monitoring clinical outcomes: a real-world first-line non-small cell lung cancer (NSCLC) prospective study

Valerio Grisitina1, Nadia Barraco1, Antonio Galvano2, Maria La Mantia1, Sofia Cutiha1, Federica Iacono1, Chiara Lisanti1, Sara Inguglia1, Delia Sardo1, Stefania Cusenza1, Alessandro Perez2, Lavinia Insalaco1, Luisa Castellana1, Tancredi Didier Bazan Russo1, Salvatore Vieni1, Fabio Fulfaro1, Lorenza Incorvaia1, Giuseppe Badalamenti1, Viviana Bazan2, Antonio Russo1

1Department of Surgical, Oncological and Oral Sciences, University of Palermo, Italy. 2Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, Italy.

BACKGROUND

Despite the increasing implementation of targeted and immune-based treatments, the prognosis of advanced non-small cell lung cancer (NSCLC) patients remains dismal. In the precision oncology era, liquid biopsy has dramatically revolutionized the management of such patients potentially overcoming tissue biopsy limitations while entering the current clinical practice as a valuable diagnostic tool. In this real-world study, we prospectively evaluated longitudinal plasma samples to investigate the potential of cfDNA kinetics as an early marker of therapeutic efficacy and predictor of prolonged survival in advanced NSCLC patients undergoing standard first-line treatments.

METHODS

This is a single-center, prospective, cohort study including treatment-naïve advanced NSCLC patients who were scheduled to receive, as per clinical practice, standard first-line treatments based on the predictive molecular pathology and clinical-pathological characteristics. Between February 10, 2020 and March 31, 2022, patients with advanced NSCLC treated at the Medical Oncology Unit of Paolo Giaccone University Hospital, Palermo Italy were consecutively recruited in a biomarker trial to assess the prognostic value of baseline cfDNA in a real-world cohort setting. For the cfDNA kinetic analysis, consecutive paired blood collection was performed at baseline (T0), at 4 weeks after the first drug administration or at the radiological response assessment within 12 weeks of the serial follow-up (T1). Blood samples were immediately processed for plasma collection and centrifuged twice (10 minutes at 3000 rpm; 10 minutes at 16,000 x g). Samples processing occurred within 1h to obtain plasma. Collected plasma specimens were stored at -80°C. From 1 to 2 ml of plasma samples were processed to isolate circulating free nucleic acids using the QiAamp Circulating Nucleic Acid kit (Qiagen). The quantitative of isolated cfDNA was assessed by QubitTM dsDNA HS Assay Kit. We used X-tile analysis to determine the optimal cfDNA cut-off value for survival prediction, randomizing two-thirds and one-third of patients as training and validation sets, respectively, according to PFS and OS.

RESULTS

Ruling out 22 patients with insufficient available plasma, 50 patients were prospectively evaluated (Figure 1). The median age was 50 (42-75) with the majority of patients being males (64%), current or former smokers (74%) while presenting with adenocarcinoma histology (75%) and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1 (92%). In the all-comers population, a baseline cfDNA cut-off value of 0.62 ng/µl for PFS and 0.61 ng/µl for OS seemed to reliably discriminate between patients with good and poor prognosis (Figures 2-3). Likewise, in the oncogene-addicted disease, we observed a baseline cfDNA cut-off value of 0.62 ng/µl for PFS and 0.54 ng/µl for OS among patients receiving Tki. Moreover, in the IO subgroup patients presenting with baseline cfDNA levels higher than 0.65 and 0.68 ng/µl seemed to experience poorer PFS and OS, respectively, when compared to patients with lower cfDNA concentrations. Patients undergoing platinum-based CT with baseline cfDNA levels higher than 0.53 ng/µl and 1.26 ng/µl showed a significantly shorter PFS (median PFS = 5.6 months; 95% CI: 4.0-7.3 months) and OS (median OS = 10.4 months; 95% CI: 6.5-14.2 months) than those with lower cfDNA concentrations (median PFS = 15.8 months; 95% CI: 10.8-20.7 months; median OS = 28.9 months; 95% CI: 5.2-52.8 months) (all p-value < 0.001).

CONCLUSIONS

In the current study, among both the all-comers population and the specific treatment subgroups, patients with higher baseline cfDNA levels showed significantly shorter median survival than those with low cfDNA concentrations. Further unbiased real-world clinical studies evaluating the putative role of serial cfDNA in the early distinction between responders versus non-responders to new treatments are warranted before a broader implementation in clinical practice.

REFERENCES