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Narrowing Time to Treatment Initiation in Non-Small Cell Lung Cancer – Cell-Free DNA Profiling at the Time of Biopsy

Perspective

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Perspective

Lung cancer is among the most common malignant diseases and currently the leading cause of cancer-related deaths in the US and worldwide [1]. The 1- and 5-year overall survival rates for lung cancer patients (47% and 18%, respectively) are far below the average cancer survival rate [2]. Due to the majority of patients being diagnosed with advanced stage of lung cancer, oncologists deem it to be one of the most relevant types of cancer to study the relationship between time-to-treatment initiation (TTI) and clinical outcome.

TTI needs to be addressed to improve lung cancer outcomes because treatment delays following diagnosis will impact patient survival [3]. In general, timely care positively affects survival of patients which are driven in part by the risk of disease progression during avoidable delays. Current clinical practice guidelines recommend time to starting lung cancer treatment ranges from 31 days to 3 months in different countries [4-7]. US guidelines to initiate treatment within 41 days of diagnosis of NSCLC. The British National Health Service (NHS) recommends treatment to initiate within 31 days of clinical decision to treat. In Norway, the recommended timeframes from receiving a referral letter to the start of treatment are 35 calendar days for systemic cancer therapy and 42 days for surgery and radiotherapy. In the Netherlands, treatment is recommended to start within 35 calendar days of the patient's first visit to a pulmonologist.

Delayed initiation of treatment could increase psychological distress and affect the prognosis for cancer patients [8,9]. A large population-based study in the US found that 36.7% of lung cancer patients experienced treatment delays (diagnosis-to-treatment interval of >35 days) [10]. Age, race, stage at diagnosis, comorbidity, and type of hospital are also associated with treatment delays [11,12].

The diagnosis-to-treatment of lung cancer patients requires complex coordination by specialized medical and surgical services, health service administrators, pathologists, testing service providers and insurance companies. The traditional approach of referring patients to different specialist consultations sequentially often results in care that is perceived as slow, fragmented, and poorly coordinated (Figure 1A). It is essential to obtain optimal clinical results in patients with suspected lung cancer to speed up the diagnostic process and early treatment as much as possible. Delays in the process, from the initial diagnosis, presentation and consultation to treatment decision may have negative consequences.

Considering the importance of an early approach in the first treatment of lung cancer, we carried out a collaborative study to implement in-parallel blood draw at the time of biopsy (for circulating cell-free DNA profiling) to expedite treatment decision-making in the earliest possible way (Figure. 1B). At the end of liquid biopsy-based sequencing test, only the confirmed lung cancer cases were included for data analysis and reported out.

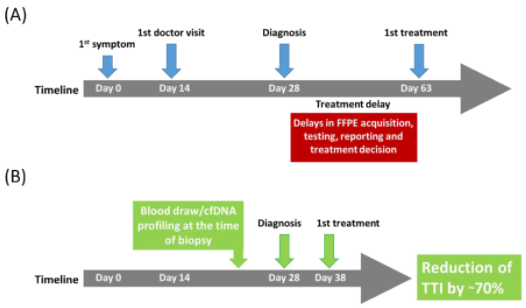

Figure 1: Timeline of (A) current tissue-only diagnosis and treatments and (B) Improved TTI by cfDNA profiling at the time of biopsy.

Genomic profiling of NSCLC patients offers the opportunity of therapeutic intervention with targeted drugs as precision medicine. The analysis of circulating cell-free DNA (cfDNA) through next generation sequencing (NGS) technology provided a powerful tool to assess actionable mutations in NSCLC patients in real time without delay. In the past few years, the identification of driver genomic alterations that represent targets for therapeutic intervention has revolutionized the management of NSCLC patients. The assessment of the mutational status of EGFR, KRAS, ALK, ROS1, RET, BRAF, MET, HER2 and NTRK plays a crucial role in the identification of the most suitable therapeutic strategy for NSCLC patients in the current clinical practice [13].

Targeted sequencing of a 100-gene NGS panel was performed to detect somatic nonsynonymous mutations present in cfDNA. The study cohort comprised 672 NSCLC patients of whom 80% were treated at community programs and 20% were received at academic institutions. As shown in Figure 2, we detected TP53 and CHEK2 mutations in 14% and 11% of the cohort, respectively, followed by GNAS (5%), BRCA2 (5%) and NF1 (5%). Mutations in POLE, RB1, ATM, KRAS, SMARCA4 and AR genes were detected in 3% each of all cases. Surprisingly, the well-known prevalent drivers such as EGFR, BRAF, PIK3CA, MET, HER2, KEAP1 and STK11 were not the commonly mutated genes in this cohort. An examination of genes implicated in DNA damage repair (DDR) pathway showed that 45% of patients had a mutation in at least one of the DDR genes.

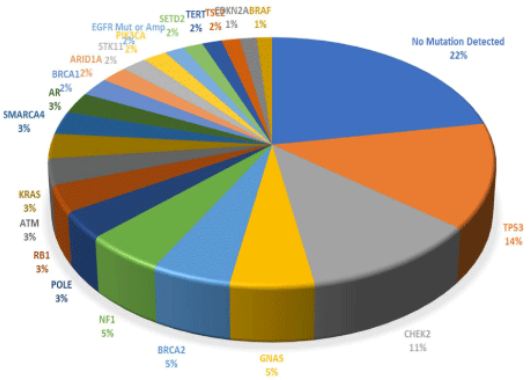

Figure 2: Mutation prevalence of detected driver genes in cfDNA of NSCLC patients at the time of biopsy.

To establish whether the mutations detected by our profiling approach could have supported the very first personalized and precision therapy, we evaluated all mutations by using the Cancer Genome Interpreter (CGI). Majority of the detected TP53 mutations were identified as cancer driver mutations and some linked to potential therapies: Decitabine (Chemotherapy), AZD6738 (ATR inhibitor), Doxorubicin (Anthracycline antitumor antibiotic), Gemcitabine (Chemotherapy), Mitomycin C (Chemotherapy), WEE1 inhibitors, Pramlintide (Amylin analogue). In addition to TP53 mutations, CGI identified cancer drivers in 67 % of samples, with 53% linked to potential therapies.

Poly-ADP ribose polymerase (PARP) inhibitors are in active development as single agents and in combination with chemotherapy across tumor types, including lung cancer [14,15]. Ongoing development of these agents already included studies focused in patients with tumors at risk for compromised DNA repair capability e.g., DDR-deficiency, for example, BRCA1/2-, ATM-, CHEK2- or POLE-mutated cancer patients. In terms of clinical utility and actionability, PARP drugs could potentially be used to treat nearly half of our cohort as the first treatment option. Most significantly, our study suggested that simultaneous blood draw at the time of biopsy is a vital step and should be implemented in current clinical practice to close TTI gap. As increased TTI is associated with increased risk of death in early-stage lung cancer, we believe such blood draw/cfDNA profiling need to be adopted more widely to diminish the potential harm to patients.

In conclusion, cancer patients require timely and effective care to ensure the best possible outcomes, and it is important to improve the diagnostic and therapeutic waiting times to which lung cancer patients are subjected, especially because time delay influences the prognosis, with the ultimate goal of increasing the cure rate and improving the quality of life and prolonging survival. NGS-based cfDNA profiling represents an effective alternative to tissue biopsy in the case of tumor tissue unavailability.

Most importantly, it also allows a comprehensive, quick turnaround and real-time characterization of the molecular landscape of the whole disease, thus providing a faithful portrait of both spatial and temporal tumor heterogeneity of NSCLC patients. Collectively, cfDNA profiling at the time of biopsy can effectively reduce TTI by about 70% over a sustained period. It is truly a single, simple and implementable solution to the issue of TTI.

References

1. Ferlay J, Soerjomataram I, Ervik M. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 v1.0. IARC CancerBase No. 11.
2. Howlader N, Noone A, Krapcho M. SEER Cancer Statistics Review (CSR) 1975-2014. 2017.
3. Anggondowati T, Ganti AK, Islam KMM. Impact of time-to-treatment on overall survival of non-small cell lung cancer patients—an analysis of the national cancer database. Transl Cancer Res. 2020; 9:1202-1211.
4. Christensen NL, Jekunen A, Heinonen S, Dalton SO, Rasmussen TR. Lung cancer guidelines in Sweden, Denmark, Norway and Finland: A comparison. Acta Oncol. 2017; 56: 943–948.
5. Guide to NHS waiting times in England.
6. Asch SM, Kerr EA, Hamilton EG, Reifel JL, McGlynn EA. RAND Corporation, Santa Monica, CA, MR-1281-AHRQ. Quality of care for oncologic conditions and HIV: A review of the literature and quality indicators. 2020; 133.
7. Hermens RP, Ouwens MM, Vonk-Okhuijsen SY. Development of quality indicators for diagnosis and treatment of patients with non-small cell lung cancer: A first step toward implementing a multidisciplinary, evidence-based guideline. Lung Cancer. 2006; 54: 117-124.
8. O'Rourke N, Edwards R. Lung cancer treatment waiting times and tumour growth. Clin Oncol. 2000; 12: 141-144.
9. Paul C, Carey M, Anderson A. Cancer patients' concerns regarding access to cancer care: Perceived impact of waiting times along the diagnosis and treatment journey. Eur J Cancer Care. 2012; 21: 321-329.
10. Kanarek NF, Hooker CM, Mathieu L. Survival after community diagnosis of early-stage non-small cell lung cancer. Am J Med. 2014; 127: 443-449.
11. Bilimoria KY, Ko CY, Tomlinson JS. Wait times for cancer surgery in the United States: Trends and predictors of delays. Ann Surg. 2011; 253: 779-785.
12. Gomez DR, Liao KP, Swisher SG. Time to treatment as a quality metric in lung cancer: Staging studies, time to treatment, and patient survival. Radiother Oncol. 2015; 115: 257-263.
13. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Correction to: "Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019; 30: 863–870.
14. Annunziata CM, O'Shaughnessy J. Poly (ADP-ribose) polymerase as a novel therapeutic target in cancer. Clin Cancer Res. 2010; 16: 4517-4526.
15. Besse B, Felip E, Barlesi F. Results of a randomized phase 2 trial of gemcitabine/cisplatin/iniparib (GCI) vs gemcitabine/cisplatin (GC) in patients with stage IV NSCLC. 14th World Conference on Lung Cancer. Amsterdam, Netherlands. 2001.