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REWIEV ARTICLE

Liquid biopsy as a source of potential biomarkers for checkpoint inhibitor treatment in non-small cell lung cancer

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Summary

Lung cancer (LC) is the leading cause of cancer-related mortality around the world. Immune checkpoint inhibitors (ICIs) have revolutionized the treatment and improved clinical outcomes of non-small-cell lung cancer (NSCLC) patients. However, while some patients have good response to ICI others are refractory to therapy or have life threatening adverse reactions. There are still no good strategies to identify responders to ICIs. That is why personalization of ICI therapy based on a patient's unique genomic profile represents an attractive strategy to improve NSCLC treatment.

There are continuous efforts to find predictive biomarkers to identify patients who are likely to respond to ICIs. In turn, these strategies are required to spare patients the time, expenses, and toxicity while trying out therapies from which they will not derive any benefit. Based on this, non-invasive liquid biopsy has the potential to help identify the patients who may respond to ICI. Liquid biopsy derived circulatory tumor DNA, circulatory tumor cells, and immune cell-based biomarkers could be new biomarkers that will guide clinical decisions for checkpoint inhibitor treatment in NSCLC. Furthermore, these biomarkers can serve for monitoring the treatment response and unraveling the mechanisms of resistance.

Keywords: immunotherapy, immune checkpoint inhibitor, biomarkers, liquid biopsy, ctDNA, circulating tumor cells, tumor mutational burden

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INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide. Non–small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. By targeting appropriate molecular targets in tumors, personalized medicine has helped improve survival in patients with NSCLC. With the advancement of technology, genetics and biomarker testing, specific biomarkers have been identified to better target treatment for individual patients who would benefit more from novel therapeutic approaches and thus have better survival (1).

Immune checkpoint inhibitors (ICI) targeting programmed cell death protein 1 (PD1) or programmed cell death ligand 1 (PD-L1) have made revolutionary changes in the clinical approach to managing NSCLC. However, only a minority of patients respond to ICI and biomarkers predicting response are still lacking (2).

Molecular, genetic and epigenetic information often stem from relatively small tissue sample which is obtained at the time of diagnosis only and which is mostly incomplete. Even at the time of diagnosis, up to 30% of NSCLC patients are unable to provide a tissue sample suitable for the foreseen molecular testing. (1). It is not always feasible for patients who are progressing on treatment rebiopsy, or it may not be suitable for molecular testing (2). Liquid biopsies provide an alternative or a complementary modality that can be utilized to better capture the molecular evolution of tumors and its spatial and temporal heterogeneity.

Various technologies and panel tests have emerged for analyzing molecular alterations for liquid biopsies. Among these, polymerase chain reaction (PCR)-based sequencing stands out, alongside the increasingly favored NGS-based sequencing methods due to their advanced capabilities.

PCR assays are a popular choice on a large scale due to their widespread use, high sensitivity, and cost-effectiveness. These technologies excel in identifying very low Mutant Allele Frequencies (MAF) of circulating tumor DNA (ctDNA). However, their limitation lies in their ability to detect only known point mutations, insertions, and deletions. That means the information about tumor DNA derived from this method is somewhat restricted. Despite this constraint, PCR-based assays are widely embraced in clinical practice for their simplicity, efficiency, and reliability.(3,4).

NGS assays have gained extensive adoption due to high sensitivity, the availability of commercial companion diagnostic and agnostic panels (capable of detecting low Mutant Allele Frequencies of circulating tumor DNA). Additionally, NGS is utilized in untargeted panels, eliminating the necessity for prior knowledge of molecular alterations and enabling the discovery of genome-wide DNA variations (5,6). NGS methods have reached a stage where both cost and performance align well with clinical diagnostic needs (7). Consequently, the increasing popularity of profiling circulating tumor DNA (ctDNA) using NGS technologies stems from their applicability throughout the entire cancer diagnosis and management process.(4).

cTDNA

Cell free DNA (cfDNA) represents extracellular strands of DNA that are present in body fluids. Specific type of cfDNA is circulating tumor DNA (ctDNA) which consists of DNA fragments that originate form tumor cells. The way in which they enter the bloodstream is not fully understood, but it has been suggested that they originate from apoptotic, necrotic tumor cells or are actively secreted via extracellular vesicles (1,8).

The major limitation for ctDNA use lies in its variable detectability (from 0.01% to more than 90%) of the total cfDNA (9). This variability depends on the type and microenvironment of the tumor, disease stage and anatomic location. However, multiple IO trials across the tumor types (including NSCLC) have validated the use of ctDNA for early diagnosis, identification of minimal residual disease, mutation detection and monitoring therapy response.

A decrease in ctDNA levels from baseline after initiation of IO therapy in NSCLC patients has been linked to immunotherapy benefit.(10). In a trial evaluating patients with advanced NSCLC undergoing pembrolizumab based therapies, a decrease in cfDNA levels at 9 weeks was associated with significantly better progression free survival (PFS) (median PFS 14.1 months v 4.4 months; hazard ratio [HR], 0.25; 95% CI, 0.13 to 0.50) and overall survival (OS) (median OS NR [95% CI lower bound 22.1 months] v 12.0 months; HR, 0.27; 95% CI, 0.12 to 0.64) (11).

Monitoring levels of ctDNA after first line of treatment is also helpful in guiding treatment decisions and monitoring disease activity as reflected in the results of IMpower010 trial that analyzed the effectiveness and safety of atezolizumab in the adjuvant setting compared to best supportive care after adjuvant platinum-based chemotherapy following resection of NSCLC (stage IB-IIIA). (12). More recently Assaf et al. reached a similar conclusion while analyzing the treatment outcomes of patients enrolled in IMpower 150 who received first-line IO-based combination therapy for advanced NSCLC. They found that patients with undetectable ctDNA levels at baseline and good ctDNA clearance derive most benefit from this treatment option in terms of median overall survival (13). Also, levels of ctDNA can help differentiate between pseudoprogression and progression as in the first case the radiographical increase in tumor size is not accompanied by the rise in ctDNA levels, while in case of progression it is (9).

An optimal treatment duration of IO therapy in advanced NSCLC patients has not been precisely established yet and is a matter of debate. Despite the fact that

most registrational studies limited the duration of IO therapy to two years, in the real-world clinical practice many patients' course of IO treatment exceeds this time frame. (14). Hellman MD et al. have found that among patients with durable response to IO therapy (>12 months) those with undetectable ctDNA at that time point have remained progression free as opposed to patients with detectable ctDNA levels whose disease ultimately progressed.(15). This concept may soon be adopted as a strategy to guide treatment de-escalation in this subset of patients.

On-treatment concentration of ctDNA could be a useful biomarker in assessing response to IO therapy. Its measurement may help differentiate those patients that are likely to benefit from IO treatment from those who are not likely to do so. It is beneficial to identify the latter in the early stages of treatment when the performance status allows for the use of other treatment regiments such as chemotherapy or perhaps targeted therapy. Identifying the former in the later stages of treatment may help reduce social, physical, and financial burden of unnecessary treatment extension.

Detection of somatic mutations in ctDNA may also serve to guide the IO treatment of NSCLC patients.

The presence of serine/threonine kinase 11 (*STK11*) mutation and a phosphatase and tensin homolog (PTEN) was associated with early progression in stage IIIb/IV NSCLC patients recieveing PD-1 inhibitors.(16) In the same study, Guibert N. et al. also found that the detection of transverse mutations in Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene and tumor suppressor gene TP53 alone in these patients lead to better outcomes.(16). Similarly, Basher et al. found that stage VI NSCLC patients receiving IO therapy with ctDNA detectable co-mutations of KRAS and STK11 had longer OS compared to patients harboring only STK11 mutation.(17). In NSCLC patients treated with IO harboring mutations in kelch-like ECH-associated protein 1 (*KEAP1*) and nuclear factor erythroid-2-related factor-2 (*NFE2L2*) genes detected in ctDNA were associated with poorer OS and PFS (18). Also, a better response and prolonged PFS were observed in NSCLC patients with AT-rich interacting domain containing protein 1A gene (*ARID1A*) mutations or AT-rich interacting domain-containing protein 1B gene (*ARID1B*) mutations while undergoing IO based therapy regiments (19). Goldberg et al. found that NSCLC patients with more than a 50% decrease in variant allelic frequency (VAF) of the detectable somatic mutation at baseline had greater PFS and OS. Interestingly, the "ctDNA response" was registered 42.5 days in median before the radiological confirmation.(20).

SOLUBLE PD1 AND PD-L1

Programmed death-1 (PD-1) is a protein found on membranes of T Cells and functions as a checkpoint. It has a key role in downregulating the immune system, advancing self-tolerance and regulating T cell exhaustion.(21). Binding of this protein to its ligand, programmed death - ligand -1 (PD-L1) inhibits T cell activation. PD-L1 is found on the surface of tumor cells and its interaction with PD-1 facilitates tumor growth through immune evasion. Development of anti-PD-1/PD-L1 antibodies has been a major steppingstone in the field of cancer immunotherapy. Since then, surface PD-L1 has been perhaps the most studied biomarker in immunotherapy. In advanced NSCLC patients undergoing anti-PD-1 based ICI therapy, higher levels of PD-L1 expression led to better OS, as per Nikolic et al. (22).

Soluble forms of PD-1 and PD-L1 can also be easily detected in peripheral circulation. Soluble PD-L1 (sPD-L1) has been studied as a potential biomarker for patients undergoing ICI therapy across tumor types including NSCLC. Elevated levels of sPD-L1 have been associated with more advanced disease and worse outcomes.(9).

In a meta-analysis by Cheng et al. including 1188 advanced NSCLC patients, authors confirmed that high sPD-L1 post treatment was significantly associated with worse OS (HR = 2.20; 95%; $p < 0.001$) and PFS (HR = 2.42; 95% $p < 0.001$) in patients treated with ICIs.(23). More recently, Schirocchi et al. reached similar conclusions in their subgroup meta-analysis of NSCLC patients. Data for OS which were pooled from five studies and included 542 NSCLC patients suggested that a higher concentration of sPD-L1 was significantly associated with worse OS (HR = 1.81; (95%CI: 1.09–3.00, $p = 0.02$). The case was similar with PFS (HR = 2.18; (95%CI: 1.27–3.76, $p < 0.01$) when the data were pooled from seven studies that included 616 NSCLC patients.(24).

In a pan-cancer cohort that included 50 NSCLC patients, high pre-treatment sPD-L1 levels were associated with advanced stage disease. Surprisingly, the sPD-L1 levels did not correlate with the tumor PD-L1 levels (25). In advanced NSCLC patients this phenomenon has been observed in other studies and the relationship between tumor tissue PD-L1 and sPD-L1 remains to be defined (26,27). It has also been observed that any on-treatment increase in sPD-1 plasma level has been correlated with improved survival for various cancers including NSCLC.(28).

With all this in mind it seems as though monitoring sPD-L1 before and throughout the IO treatment may help in selecting patients that are likely to benefit from it. However, further effort is needed in the domain of standardization of sPD-L1 sampling and its quantifying before this potential biomarker can be further validated in large scale trials.

BLOOD CELL COUNT AND NEUTROPHIL TO LYMPHOCYTE RATIO

Peripheral blood cell counts and their ratios have also been evaluated as biomarkers for the response to immunotherapy in NSCLC patients.

Low concentration of circulating lymphocytes may correlate with lower levels of tumor-infiltrating lymphocytes (TILs) and a diminished anti-tumor T-cell response (29). Neutrophil to lymphocyte ratio (NLR) reflects systemic inflammation and could provide insight into balance of the immune system in a patient with a malignant neoplasm (30,31). The fact that these analyses are easily accessible (in a sense that they can be obtained via simple blood test that is available anywhere in the world), cost-effective and reliable make them an attractive biomarker candidate.

Ye Jin Lee et al. found that increased pre- and post-treatment peripheral lymphocyte count in NSCLC patients undergoing ICI therapy was associated with favorable PFS and OS (32).

A meta-analysis that included 1225 NSCLC patients on nivolumab from 14 retrospective studies concluded that elevated pretreatment NLR was associated with poor PFS (HR = 1.44; 95% confidence interval (CI):1.18–1.77; $p < 0.05$) and OS (HR = 1.75; 95% CI: 1.33–2.30; $p < 0.05$).(33).

More recently another meta-analysis evaluated NLR in 1719 advanced NSCLC patients undergoing IO therapy and a similar conclusion was made. Elevation of NLR at baseline as associated with worse outcomes, both in PFS and OS (HR PFS 2.21 [95% CI: 1.50–3.24; $p < 0.0001$] and HR OS 2.68 [95% CI: 2.24–3.6; $p < 0.0001$) (34).

NLR ratio as a prognostic indicator is not unique to ICI-treated patients as NLR may be a prognostic indicator for different cancer treatment modalities as well as other conditions.(9). Also, there are plethora of factors that may influence and distort NLR such as age, gender, ethnic, environmental factors and lifestyle (34). While cut-off value for NLR of 5 has been used in most of the studies in the aforementioned meta-analyses, it is yet to be standardized and thus find its way into the daily clinical practice.

TMB

The overall count of somatic mutations occurring within one million bases of DNA (1 megabase, Mb), referred to as tumor mutational burden (TMB), plays a significant role in predicting how well a patient responds to immunotherapy (IO) in various types of cancer. Elevated TMB can stem from various biological processes, including the exposure to environmental factors like cigarette smoke or ultraviolet radiation. It can also arise from harmful mutations in mismatch repair genes leading to microsatellite instability or in the DNA repair system. These factors collectively influence the TMB and consequently impact the effectiveness of immunotherapy treatment.

Although tissue biopsy remains a standard for TMB assessment, obtaining sufficient tissue from advanced cancer patients is challenging, and archived primary tumor samples might not fully represent the evolving tumor during advanced stages. In such cases, a minimally invasive approach using ctDNA-based TMB becomes crucial to identify patients who may benefit from ICI immunotherapies. Some studies show good agreement between ctDNA-based TMB and tissue TMB, suggesting that cTMB testing is feasible and predicts the outcomes of IO therapies.

To better determine which patients will respond positively to IO treatments, more research is required to establish specific cutoff values for cTMB and tTMB and fully evaluate the predictive value of cTMB.

To determine the tumor mutational burden (TMB), a considerable number of genes, usually more than 300, need to be sequenced. The purpose is to analyze these genes and calculate the number of non-synonymous mutations per mega base pair (Mbp). Researchers are currently investigating the potential association between TMB, specifically ctDNA-based TMB (cTMB), and clinical outcomes in various studies like BF1RST, MYSTIC, and OAK trials (30-32).

Overall, patients with detectable ctDNA and higher cTMB at the time of diagnosis (greater than 10–16 mutations per Mbp) tend to experience a longer median overall survival (OS) when treated with first-line immune checkpoint inhibitor (ICI) therapy. It was observed that patients with less than 10 mutations per Mbp detectable from ctDNA did not benefit significantly from immune checkpoint inhibitor treatment in this study.

High cTMB (ctDNA-based TMB) predicts better responses to immune checkpoint inhibitor (IO) treatments compared to chemotherapy. The greater the number of mutations per mega base pair (Mb) at a cutoff of ≥20, the more significant the benefit is when using IO therapies.

However, in some studies, the agreement between cTMB and tTMB (tissue-based TMB) for the patients involved was low. This difference could be due to varying amounts of ctDNA released by the tumor and normalizing for ctDNA versus cfDNA might enhance the reliability of cTMB. Additionally, technical variations arising from different methods of ctDNA isolation and sequencing could also lead to discrepancies in genomic coverage.

A high TMB is generally defined as having at least 10 mutations per Mb. However, the determination of TMB can vary significantly depending on whether panel sequencing (with more than 300 genes) or whole exome sequencing is used, necessitating adaptation of the TMB score based on the sequencing method. Through clinical validation efforts, researchers have determined specific TMB cutoff values that can predict the response to ICI treatment. This demonstrates that TMB is an independent predictive biomarker, complementing other markers like PD-L1, for assessing the effectiveness of ICI therapy (27).

For instance, in the NSCLC CheckMate-227 trial, it was evident that higher TMB levels predicted longer progression-free survival (PFS) in patients receiving a

combination of nivolumab and ipilimumab, but it did not show the same benefit in patients receiving chemotherapy alone (28).

Furthermore, elevated TMB was also found to be a predictor of improved survival in patients with various types of tumors receiving ICI treatment. However, the specific TMB cutoff values varied significantly depending on the type of cancer being treated.

TISSUE OR LIQUID? BOTH?

Acquiring a tissue sample is often imperative for a conclusive diagnosis and the identification of tumor histology. Additionally, as previously mentioned, tissue sample is the standard for TMB assessment as well as PD-L1 tumor proportion score. Tumor heterogeneity, both spatial and temporal, make accurate assessment of resistance and driver mutations based on biopsy of a single metastatic site challenging. Liquid biopsy with its capacity to address these challenges and provide a faster turnaround time, emerges as a potential complement and even an alternative in certain scenarios. Good concordance between the two methods and the high specificity and the moderate sensitivity of liquid biopsies has been established across cancer groups including NSCLC.(35–37)

In a prospective study of 323 advanced NSCLC patients, Aggarwal et al. found that in case of inadequate tissue DNA, liquid NGS biopsies are an adequate surrogate for molecular profiling. They found therapeutically targetable mutations were detected in 113 patients (35.0%), 66 (58.4%) had a mutation in plasma and there were only 8 patients that had negative concurrent tissue tests carried out. Furthermore, 101 patients in the mentioned study tissue testing was not possible highlighting the importance of liquid biopsy as an adequate alternative.(36).

CONCLUSION

Newly developing predictive biomarkers for immune checkpoint inhibitors (IO) encompass the evaluation of PD-L1 expression on circulating tumor cells (CTCs) and/or peripheral blood mononuclear cells (PBMCs), as well as the assessment of tumor mutational burden (TMB). However, the reliability of predicting patient responses using these biomarkers is still uncertain, similar to tissue-based markers, often due to technical limitations in terms of sensitivity and specificity. Overcoming these challenges is crucial in order to enhance and ensure the reproducibility of these biomarkers, ultimately improving their effectiveness in predicting treatment outcomes.

Using a comprehensive genomic profiling (CGP) approach offers the benefit of generating combined biomarkers. These composite biomarkers can help categorize patient groups more effectively, identifying those who are most likely to experience significant clinical benefits from immune checkpoint inhibitors and other targeted treatments that are matched to their specific genomic profiles.

Conflict of interest

None to declare.

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NEINVAZIVNA TEČNA BIOPSIJA KAO IZVOR POTENCIJALNIH BIOMARKERA ZA LEČENJE NESITNOĆELIJSKOG KARCINOMA PLUĆA INHIBITORIMA KONTROLNE TAČKE

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Sažetak

Karcinom pluća (LC) je vodeći uzrok smrtnosti od malignih bolesti širom sveta. Iako je terapija inhibitorima imunoloških kontrolnih tačaka (ICI) dovela do revolucije u lečenju i poboljšanju kliničkih ishoda pacijenata obolelih od nesitnoćelijskog karcinoma pluća (NSCLC) i neki pacijenti imaju dobar odgovor na nju, drugi su rezistentni na ovu terapiju ili imaju neželjena dejstva opasna po život. Još uvek ne postoje dobri biomarkeri za predikciju odgovora na ICI. Zato personalizacija ICI terapije na osnovu jedinstvenog genomskog profila pacijenta predstavlja atraktivnu strategiju za poboljšanje ishoda lečenja bolesnika sa NSCLC.

Postoje kontinuirani napori da se pronađu prediktivni biomarkeri za selekciju pacijenata koji će reagovati na ICI, sa ciljem da se izbegne gubitak dragocenog vremena, troškova i toksičnosti pri isprobavanju terapija od kojih pacijent neće imati nikakve koristi.

Neinvazivna tečna biopsija ima potencijal da pomogne u otkrivanju pacijenata koji mogu da reaguju na ICI. Utvrdjivanje cirkulišuće DNK tumora, cirkulišućih tumorskih ćelija i drugih biomarkera iz tečnih biopsija mogli bi da budu novi biomarkeri koji će uticati na izbor ICI u lečenju NSCLC. Pored toga, ovi biomarkeri mogu da posluže za praćenje odgovora na tretman i otkrivanje mehanizama rezistencije.

Ključne reči: imunoterapija, inhibitori kontrolne tačke, biomarkeri, tečna biopsija, ctDNA, cirkulišće tumorske ćelije, TMB

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