Review Article

Central nervous system progression and liquid biopsy in patients with oncogene addicted non-small cell lung cancer treated with ALK/ROS1 inhibitors

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Abstract: Non-small cell lung cancer (NSCLC) driven by *ALK* or *ROS1* rearrangements have an increased risk for developing central nervous system (CNS) metastases, as a result of increased CNS tropism of the tumor cell or insufficient drug penetration of the blood-brain barrier. Novel generation tyrosine kinase inhibitors (TKIs) have increased intracranial activity after failing crizotinib or in the frontline setting. The sequential use of TKIs is effective in controlling CNS disease and patients may attain long-term survival, despite the presence of CNS disease. Disease progression under TKIs is frequently associated with the development of resistance mutations, which need drugs that do not have the same resistance profile. Tailoring treatment according to resistance alterations might increase the chance of obtaining a response, which is essential for patients at risk of rapid clinical deterioration, such as those with CNS disease. Moreover, the molecular portrait of CNS metastases might differ than that of extra-CNS metastases. The molecular characterization of the CNS disease is challenged by the invasive nature of tissue biopsies and the risk of negative liquid biopsies when performed in plasma. The analysis of the cerebro-spinal fluid (CSF) by liquid biopsy has proven to be more sensitive than plasma for the detection of genomic alterations in patients with CNS progression. Here, we discuss the interest and feasibility of performing a liquid biopsy to characterize CNS metastases of NSCLC patients treated with ALK and ROS1 inhibitors.

Keywords: *ALK; ROS1*; brain; meningeal; liquid biopsy; circulating tumor DNA (ctDNA)

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Introduction

Oncogene-addicted non-small cell lung cancer (NSCLC) patients frequently develop central nervous system (CNS) metastases, with percentages reaching up to 50% for brain and 10% for leptomeningeal metastases (1-3). *ALK*- and *ROS1*-positive tumors have a high CNS tropism, with an incidence of CNS metastases at baseline of 36% and 34%, respectively (4), a risk of CNS progression of 58% at 3 years (5) and up to 70% at progression during crizotinib treatment (1,6,7). Also, in a significant proportion of cases, patients develop isolated CNS metastases, especially when

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treated with first-generation tyrosine kinase inhibitors (TKIs), due to an insufficient drug penetration of the blood-brain barrier (4,8,9).

CNS metastases are associated with a dismal prognosis and impact the quality of life of cancer patients, which highlights the importance of administering an effective treatment for CNS disease. Novel generation TKIs, including second (alectinib, ceritinib, brigatinib) and third generation (lorlatinib) ALK and ROS1 inhibitors proved an increased intracranial activity with long duration of responses (10).

The use of TKIs frequently result in the development of on-target or by-pass resistance alterations. In *ALK*-rearranged NSCLC, *ALK* mutations occur in 30% of patients under crizotinib, in up to 54–70% after second generation ALK inhibitors and may accumulate with the sequential use of TKIs (11,12). There is a wide spectrum of resistance alterations that have their own sensitivity and need drugs with different structures, that do not have the same resistance profile (13). Similarly, *ROS1*-rearranged NSCLC may develop various resistance mutations under crizotinib, which may have different sensitivity profiles for newer generation inhibitors (14). Thus, the identification of resistance alterations might better guide treatment choice and tailor treatment according to the "sensitivity profile" of each alteration. This might increase chances of using the most adequate treatment, which is essential for patients with CNS progression, at risk of rapid neurological deterioration.

However, obtaining a molecular profile of the CNS progression is challenged by the invasive nature of tissue biopsies, which are not feasible in the majority of cases. An alternative technique is the analysis of circulating tumor DNA (ctDNA), which is shed by tumors in the blood or other liquids, such as the cerebro-spinal fluid (CSF), pleural or peritoneal collections. ctDNA analysis, named "liquid biopsy" is a minimally invasive technique, that may detect genomic alterations and resistance mutations with high sensitivity and specificity (15,16).

Here, we discuss the interest and feasibility of liquid biopsy in patients with *ALK*- or *ROS1*-rearranged tumors with CNS metastases.

TKIs and CNS metastases

In *ALK*-rearranged NSCLC, crizotinib, the first approved ALK inhibitor, has superior intracranial disease control rates compared to standard chemotherapy, but the insufficient CNS penetration of crizotinib leads to that CNS is the main site of disease progression (7,17). Next-generation ALK inhibitors have superior intracranial activity compared to crizotinib and/or chemotherapy, with early and durable CNS responses (18-26). Importantly, second generation ALK inhibitors have also an intra-cranial activity after crizotinib failure, while lorlatinib, a third generation TKI inhibitor, is active also in heavily pre-treated patients who fail at least two lines of therapy (27). Lorlatinib is very active in patients with CNS disease because of its high CNS penetration that reach 75% of plasma levels in the CSF, and because it is able to treat the majority of *ALK* resistance mutations (27,28).

In *ROS1*-rearranged NSCLC, ROS1/ALK inhibitors are highly active, including in patients with brain metastases. Crizotinib, the first approved ROS1 inhibitor, showed an objective response rate of 71.7%, regardless of the presence of brain metastases at baseline. In 23 patients with measurable brain metastases at baseline, the median progression-free survival (PFS) was 10.2 months (29). In crizotinib-naïve patients with baseline brain metastases, next generation ROS1 inhibitors have increased intracranial activity, as reported with ceritinib in 5 out of 8 patients in a phase II study (30) and entrectinib, an ALK/ROS1/pan-TRK inhibitor, in 55% of patients in a pooled analysis of phase I and II studies (31). Repotrectinib, another next generation ROS1/TRK/ALK inhibitor, was shown to have intracranial activity in *in vivo* and clinical studies (32,33). In crizotinib-pretreated NSCLC patients with baseline CNS metastases included in the IFCT-1803 LORLATU expanded access program cohort, lorlatinib showed intracranial ORR of 37.7%, similar to *ALK*-positive patients (34).

Tailoring treatment based on the molecular profile might improve patients' outcomes

As next generation ALK and ROS1 inhibitors have different "sensitivity" profiles (10,14,32,35,36) (*Figure 1*), a tailored treatment based on the identified resistance mutations might gain additional lines of therapy, while also increasing the chance of obtaining a CNS response. In case of *ALK*-positive tumors, lorlatinib may be effective in the majority of cases, especially when the *ALK* G1202 mutation is found, which is resistant to all other ALK inhibitors and it is the main resistance mutation after the current standard of care, second generation TKI (13). Promising preclinical data presented at AACR 2020 point out towards TPX-031, a novel ALK inhibitor, with high potency against the wild-

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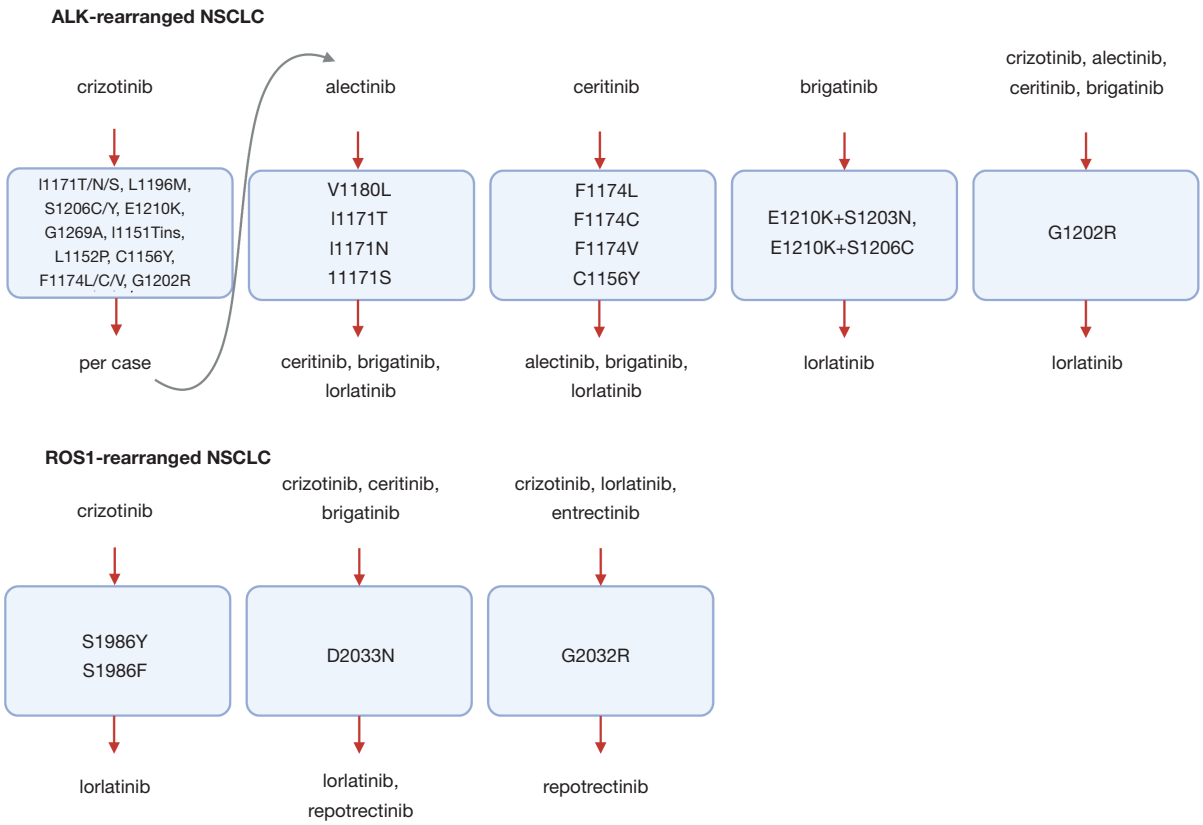

Figure 1 Examples of treatment tailoring based on the identification of resistance mutations. NSCLC, non-small cell lung cancer.

type *ALK* and hard to treat mutations, such as the solvent front mutation G1202R and the compound mutation G1202R/L1196M. In case of *ROS1* positive tumors, the identification of *ROS1* G2032R could directly tailor patients for the use of repotrectinib and not lorlatinib, which will not be active in this situation (32). The identification of compound mutations that drive resistance to third generation inhibitors, might be overcome in selected cases by first or second-generation inhibitors with different molecular structures or they might even resensitize tumors to first generation inhibitors (37,38). Also, emergent bypass alterations might benefit from personalized drug combinations, such as dual *ALK/MET* blockade in tumors acquiring *MET* alterations (39).

Clinical trials evaluating drugs matched to the identified resistance alterations will help clarify the clinical utility of a personalized approach. For instance, the ongoing National Cancer Institute (NCI)-NRG ALK Protocol phase II randomized trial (NCT03737994) investigates the use of tumor and liquid biopsies in 660 *ALK*-positive NSCLC patients failing a next-generation inhibitor, who receive a matched treatment according to the identified resistance mutation. The ALKALINE (NCT04127110) and the ORAKLE (NCT04111705) phase II studies aim to assess the clinical activity of lorlatinib in NSCLC patients failing second generation inhibitors, based on the molecular pattern of resistance to prior ALK inhibitors, assessed by liquid biopsy and tissue or liquid biopsy, respectively.

Clinical relevance of liquid biopsy in the characterization of CNS lesions

As performing CNS tissue biopsies is highly invasive for the patient, liquid biopsy by ctDNA appears as an easy, minimally invasive technique, able to rapidly provide a tumor molecular profiling (15).

In *ALK*-positive NSCLC, plasma liquid biopsy has been proven to be clinically relevant at detecting the fusion and resistance mutations after failing TKIs. In 101 NSCLC patients positive for the *ALK* fusion, targeted

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next-generation, amplicon-based sequencing has shown a sensitivity of 67% for the fusion detection at baseline and 46% at TKI failure. Resistance mutations following TKIs were detected in 22% of *ALK*-positive cases at progression to first and next generation ALK TKIs (29% after second generation ALK TKI), with *ALK* G1202R the most frequently detected. Interestingly, the authors studied the efficacy of the next therapy based on the presence of molecular alterations in blood. The presence of resistance alterations was associated with an overall survival of 58.5 months in case of *ALK* mutations and 44.1 months in case of other alterations. A negative liquid biopsy (no alteration detected) at TKI failure was associated with improved outcomes (105 months), that may be related to the low tumor burden of these patients. Among patients with *ALK* mutations, patients harboring complex *ALK*-resistance mutations had the poorest outcomes to next therapy (40). In another study on 76 ALK-positive NSCLC, a high concordance of the *ALK* fusion was obtained between plasma and tissue in 91% of cases (20/22 blood/tissue samples). In 15 patients failing a TKI, 24 *ALK* resistance mutations were detected, the most commonly observed being *ALK* G1269A (4/24 alterations) (41).

In 27 *ROS1*-positive NSCLC, plasma liquid biopsy by amplicon-based sequencing identified resistance mutations following TKIs in 30% of *ROS1*-positive cases, with *ROS1* G2032R being the most frequently detected. Similar to ALK, a negative liquid biopsy at TKI failure was associated with improved outcomes, and the presence of G2032R at progression to crizotinib was associated with rapid progression to subsequent therapy, including lorlatinib (40). Similar results were obtained in 56 *ROS1*-positive NSCLC, where the detection of the *ROS1* fusion at relapse following ROS1 inhibitors was 50% by plasma liquid biopsy. Six out of 18 patients failing crizotinib (33%) had *ROS1* resistance mutations, the most frequently detected being the *ROS1* G2032R mutation, in 5 out of 6 cases (42).

However, plasma liquid biopsy is unlikely to adequately characterize the molecular landscape of CNS metastases, as the blood-brain barrier could reduce the presence of ctDNA in the bloodstream. Our group has evaluated the clinical relevance of plasma liquid biopsy in oncogene-addicted NSCLC with isolated CNS progression, in comparison with patients with systemic progression. Although we used a highly sensitive next-generation sequencing assay, there was a high percentage of negative liquid biopsies in patients with isolated CNS progression (48%), as opposed to patients with systemic progression (8–16%). In several patients with longitudinal biopsies, a negative liquid biopsy at the moment of isolated CNS progression shifted to positive when there was a systemic progression. Moreover, patients with isolated CNS progression and positive liquid biopsies had a higher chance of developing earlier a subsequent extra-CNS progression, suggesting that plasma ctDNA was more likely to be shed by infra-radiologic, active extra-CNS lesions (9).

A more suitable way for characterizing the mutational landscape of CNS lesions is the CSF (43). As compared to plasma ctDNA, several studies have shown that CSF ctDNA had a higher mutation detection rates and higher allele frequencies of identified genomic alterations in a cohort of 72 NSCLC patients (44), in 26 *EGFR* driven-NSCLC (45) and 11 *ALK* rearranged NSCLC patients with leptomeningeal metastases (3). In the 11 paired plasma-CSF samples from *ALK* rearranged NSCLC patients, the driver alterations were detected in 9 out of 11 CSF samples (81.8%) and in 5 out of 11 plasma samples (45.5%). In one patient, two ALK resistance mutations were detected in CSF and not in plasma (3). Moreover, a significant number of unique mutations was found in CSF, such as copy number variants of *EGFR*, *CCND1*, *FGF3* and *FGF4* (3). Similarly, in a cohort of *EGFR*-driven NSCLC with leptomeningeal disease, acquired resistance alterations, such as *EGFR* T790M, copy-number variants of *MET*, *ERBB2*, and *KRAS*, and *TP53* loss of heterozygosity, were detected in CSF ctDNA compared to plasma ctDNA, which mainly detected the initial *EGFR*-activating mutations (45). This could be explained by the fact that alterations with low allele frequencies might be easier detected in CSF where the low levels of non-tumor derived DNA lead to a high ctDNA/circulating free DNA ratio (46). Also, differences in tumor genomics could occur between the CNS and extra-CNS lesions because of reduced CNS drug penetration which could determine a different tumor selection in the CNS (47). This might explain the variable prevalence of *EGFR* T790M which has been reported within studies. In the study of Li *et al.*, *EGFR* T790M was detected in 30.4% in CSF versus 21.7% in plasma after TKI progression at leptomeningeal metastasis diagnosis (45), while Ying *et al.* reported a higher *EGFR* T790M mutation detection rate in plasma than in CSF (15.3% plasma *vs.* 2.8% CSF, P=0.017) in 72 NSCLC patients with leptomeningeal metastases (44). In another study, *EGFR T790M* was rarely found in CSF at diagnosis of leptomeningeal metastases in patients exposed

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to TKI, in more cases under erlotinib than under gefitinib, suggesting that the emergence of resistance mutation might be correlated with the CSF concentration of first generation TKI (48).

While the relevance of CSF liquid biopsy is supported by several studies in patients with leptomeningeal metastases, less is known about its utility for patients with brain metastases. In 66 treatment naive NSCLC patients, Li *et al.* recently investigated the phenotypical features of brain metastases to predict the probability of detecting ctDNA in CSF. After considering tumor size and distance to ventricles, authors established a prediction model to select patients for CSF analysis with AUC 0.82, sensitivity of 90.6% and specificity of 73.9% (49). This work aimed to avoid invasive procedures (lumbar punctures) in patients with low chances of having a positive liquid biopsy. However, in addition to the amount of ctDNA that is shed in the CSF, the sensitivity of the liquid biopsy technique would also have an important contribution.

In addition to the molecular profile, another factor that should be considered at progression is the TKI concentration. In an exploratory cohort of 41 patients with oncogene-addicted NSCLC patients treated with TKI, the plasmatic TKI concentration at progression was lower than normal in 57% (n=21/37 samples) of cases, including 3 out of 4 patients with isolated CNS progression (50).

Unanswered questions and future perspectives

Could plasma liquid biopsy still be useful in case of isolated CNS progression?

The absence of any identified genomic alteration in a plasma liquid biopsy in an oncogene-addicted NSCLC patient with isolated CNS progression should be interpreted as a false negative result, most probably caused by an insufficient plasmatic ctDNA. In the absence of known drivers, aberrant ctDNA methylation may help to accurately identify and quantify ctDNA with respect to normal circulating free DNA (51). When the plasma liquid biopsy is found to be positive and genomic alterations are identified, it may reveal the molecular profile corresponding to the CNS progression but it may also predict for a subsequent extra-CNS progression (9). It would be interesting to evaluate this observation in prospective studies, as it may prove to be useful in the selection of CNS progressing patients for brain irradiation or for the switch of systemic therapy.

Could CSF liquid biopsy evaluate response to treatment in case of leptomeningeal disease?

The evaluation of treatment response in case of leptomeningeal meningitis is evaluated by radiological findings, CSF cytology and clinical evolution of neurological signs and symptoms (52). However, this is less precise than in case of brain metastases and often difficult to perform, especially in the absence of typical radiological findings. It may be interesting to investigate CSF liquid biopsy as a potential tool to evaluate response to treatment or even to guide subsequent therapeutic strategies in case of isolated leptomeningeal progression.

Conclusions

CNS progression is a common event in patients with *ALK* or *ROS1* positive NSCLC. The molecular characterization of CNS disease can be performed by liquid biopsy, the most accurate being the CSF analysis. Tailoring treatment based on the molecular profile may improve patients' outcomes and possibly lower the risk of rapid CNS deterioration as compared to a "blinded" treatment switch, currently under evaluation in prospective studies.

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