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theme :
INCREASING PULMONOLOGY COMPETENCE
TO STRENGTHENING
COMPETITIVENESS IN SDGs ERA

September, 11th - 16th, 2019

Alila Hotel Solo

KUMPULAN MAKALAH

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TREATMENT STRATEGIES IN ALK-POSITIVE NSCLC

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ABSTRACT

Non-small cell lung cancer (NSCLC) is now regarded as a complex malignancy and its molecular and genomic diversity allows for personalized treatment options. The development of genomic-based characterization of lung cancer had shifted the focus of treatment from cytotoxic chemotherapy and radiation treatments to a newer targeted therapeutics that can overcome the limitations of previous treatment modalities. It was started by the discovery of various genetic driver mutations such as gain-of-function EGFR and KRAS mutations, ALK and ROS1 translocations, andMET amplifications/mutations which lead to the development of several tyrosine kinase inhibitors (TKIs).ALK-positive NSCLC represents a distinct molecular subtype, which is often mutually exclusive with EGFR mutations or K-RAS mutations. Fluorescence in situ hybridization (FISH) is used as the diagnostic test for detecting an EML4–ALK rearrangement. It is more common among adenocarcinoma patients with certain characteristics.

The development of crizotinib had revolutionized the treatment for ALK positive NSCLC. The results of PROFILE studies had led to the accelerated approval of this first-generation ALK inhibitor by the US FDA in 2011. Unfortunately, in mostpatients the cancer progressed within the first 12 monthsdue to the emergence of acquired resistance to crizotinib. Novel approaches to overcome crizotinib-acquired resistance had been reported. Second-generation of ALK inhibitors such as Ceritinib, Alectinib, and Brigatinib subsequently developed and approved. As with EGFR-TKI, resistance to second-generation ALK inhibitor

emerge as well. Third-generation of ALK inhibitor with activity against EML4-ALK enzymes and almost all its mutant forms, including the ones that drive resistance to Ceritinib and Alectinib, such as Lorlatinib, Entrectinib, and many other new compounds are currently under clinical investigations. Based on the results and evidents derived from those clinical trials, treatment strategy for ALK-positive NSCLC can be proposed, applying sequential therapy with all the available active ALK-inhibitors.

INTRODUCTION

Lung cancer is the most common killer cancer worldwide.[1] Most of lung cancers (~90%) are NSCLC.It is consisted of three main subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is the most common subtype of NSCLC, comprising approximately 40% to 50% of all lung cancer.[2]Each NSCLC subtypes are driven by various activated oncogenes. Currently, at least eighteen different driver mutations have been identified in NSCLC.In 2004, for the first time, mutations in the epidermal growth factor receptor (EGFR) gene were described in some advanced cases of NSCLC. This kind of mutation responds very well to treatment with EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib.[3]Several years later, a small inversion/translocation in chromosome 2p, resulting in a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene, had been described in a subset of advanced NSCLC.[4]

Anaplastic lymphoma kinase (ALK) is a fusion oncogene.ALK rearrangements occur in 3–7% of patients with NSCLC and are more common among patients with a never/light smoking history, adenocarcinoma histology, a younger age, female gender and in tumours wild type for EGFR and KRAS.[5,6]It is largely mutually exclusive of EGFR or K-RAS mutations.[5] At least 27 fusion variants have been identified according to the specific chromosomal location of the gene fusion.[7] The prevalence of ALK mutations in NSCLC patients is similar across different races.[8]International Association for the Study of LungCancer (IASLC) and the European Society forMedical Oncology (ESMO)

recommend all patientswith advanced-stage lung adenocarcinoma ortumours with an adenocarcinoma component,should be tested for ALK irrespective of clinical characteristics.

Crizotinib was the first ALK inhibitor approved by the US FDA,[9] but soon, most patients develop resistance to this drug. Following it several new generation of ALK inhibitors had been developed and subsequently approved such as Ceritinib, Alectinib, Brigatinib,[10]Entrectinib,[11] and Lorlatinib,[12] as second and third generation ALK inhibitors. Updated guidelines are available for the choice of ALK inhibitors based on the latest evidences. This short article will describe the methods for ALK rearrangement detections, first-line treatment choice for ALK positive NSCLC, resistance to TKIs and its mechanisms, and subsequent therapies for progressive cases.

DETECTION OF ALK REARRANGEMENTS IN NSCLC PATIENTS

EML4-ALK rearranged NSCLC harbor a chimeric fusion gene involving ALK. This fusion results from the rearrangement within chromosome 2 [inv (2)(p21p23)] and fusion of the 5' portion of EML4 with the 3' portion of ALK. So far there have been at least 14 variants of the EML4-ALK fusion gene reported, which contain varying lengths of EML4 and encode the cytoplasmic portion of ALK protein.

All patients with advanced NSCLC, with the exclusion of pure squamous cell carcinoma in former or current smokers, should be tested for ALK rearrangements. As mentioned earlier, considering that the EGFR mutation and ALK rearrangement are mutually exclusive, panel of experts agreed that for those patients with 1 known mutation, routine testing for the other is not required.

There are several molecular ALK mutation testing methods; the most common are immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), and polymerase chain reaction based techniques (PCR). Each have their respective advantages and disadvantages.[13]Reverse transcription polymerase chain reaction (RT-PCR)-based detection is considered more sensitive and reliable approach compared to FISH and IHC. ALK FISH is clinically validated, but the assay can be technically challenging.[14]

FISH

The gold standard for ALK NSCLC mutattion testing is FISH analysis. In 2011 the Abbot Vysis ALK Break Apart FISH Probe Kit is approved by the FDA for molecular diagnostic testing. The unstained tissue should be hybridized overnight with the ALK probe and then evaluated by fluorescence microscopy. When the ALK probe shows separated red and green fluorophores or has loss of the green signal in 15% or more of the cells examined, an ALK translocation is regarded as positive. FISH analysis for EML4-ALK translocations has several disadvantages, i.e.: it has a high cost,its interpretation requires expertise and experience, it does not identify specific translocation types, and often has a lengthy turn-around time.[13]The advantages of FISH are that it can detect all ALK rearrangements regardless of the fusion partner and is accurate and reliable.

Immunohistochemistry (IHC)

There is currently no standard protocol for using IHC to detect ALK in NSCLC. Furhtermore, ALK protein levels in ALK-rearranged NSCLCs are considerably low. Antibodies used with some success have been D5F3 (Cell Signaling Technology, Danvers, MA, USA), 5A4 (Novocastra, Newcastle, UK), and ALK clone ZAL4 (Invitrogen, Carlsbad, CA, USA).[13]The advantages of IHC technique are: low cost, ease of interpretation by the general pathologist,retention of histologic information, relative short turn-around time, and relative ease of implementation. The disadvantages of this technique include: problems in tissue preparation,antibody choice, signal enhancement systems, and the optimal scoring system. The clinical application of ALK IHC in NSCLC need further analysis and validation.[13,14]

Reverse transcription polymerase chain reaction based techniques (RT-PCR)

PCR-based techniques can detect ALK expression in NSCLC. RT-PCR is a precise, sensitive, and reproducibletechnique to detect the transcripts of EML4-ALK fusion.More over, the amplicons can be sequenced toidentify the specific fusion variants. First, the RNA is converted into cDNA by

reversetranscriptase, and then the cDNA is PCR amplified with specificprimers. Primer sets specific foreach translocation is required for amplification. Several commercial kits areavailable which usually have primers to most or all of theEML4-ALK fusions transcripts. The amplicons can be identified by a variety of methods,including sequencing, electrophoresis, fluorescent probe degradation,and NanoString nCounter capturetechnology.[15,16]

ALK INHIBITORSIN THE TREATMENT OF ALK POSITIVE NSCLC

Shortly, after the discovery of ALK rearrangements in NSCLC, it was recognized that these confer exquisite sensitivity to ALK inhibition. Crizotinib is the first ALK/ROS1/MET inhibitor that had been developed. Its activity was specifically tested in 149 ALK+ advanced NSCLC patients in a phase I study. Impressively, Crizotinib yielded a high obective response rate (60.8%) in this selected population. Obective responses were rapid and durable, with progression free survival (PFS) of 7 to 10 months.[17]In subsequent phase III trials (PROFILE 1014 and 1007), Crizotinib showed significant improvements in objective response rate (ORR), PFS and quality of life compared to first- and second-line chemotherapy. These results lead to FDA approval in 2011 for the treatment of advanced ALK-positive NSCLC, initially as second-line treatment, and then as the standard first-line therapy in 2015.[18]

However, not long after initial response to Crizotinib, in most patients the cancer inevitably relapse. The central nervous system (CNS) is a frequent site of relapse. The mechanisms of acquired resistance to Crizotinib can be divided into 2 classes, ALK dependent or ALK independent. The first mechanism involves the development of secondary mutations in the kinase target or via gene amplification of the kinase itself, that facilitates preserved downsteam ALK signaling. Several types of secondary mutations had been identified such as L1196M and G1269A. The second mechanism includes bypass pathways that can be activated in some resistant cells, cKIT gene amplification, concomitant EGFR-activating mutation or KRAS mutation, and insulin-like growth factor 1 receptor (IGF1R).[19]

Second generation ALK inhibitors, which are more potent than Crizotinib, subsequently developed and might be effective in re-inducing remissions when cancers are still addicted to ALK. Ceritinib and Alectinib are approved for patients with metastatic ALK positive NSCLC. Brigatinib is gaining accelerated approval by United States FDA. The efficacy of Ceritinib which is 20 times more potent than Crizotinib was supported by two trials, phase 1 ASCEND-1 and phase 2 ASCEND-2.[20,21] Objective response rate (ORR) in ASCEND-1 was 56% with median PFS of 6.9 months,[20] while in ASCEND-2 the ORR was 35.7%, the median PFS was 7.2 months, and median overall survival (OS) was 1.9 months.[21] Ceritinib has documented efficacy against Crizotinib-resistant ALK such as L1196M, G12696M, I1171T, and S1206Y.[22] The efficacy of Alectinib was supported by two trials, phase 2 NP28761 with ORR of 40.2%, median PFS of 8.2 months, and median OS of 22.7 months;[23] and phase 2 NP28673 with ORR of 44.9%, median PFS of 8.9 months, and median OS of 26.0 months.[24] Support for the efficacy of Brigatinib was originated from one phase 2 trial, ALTA which showed ORR of 54.5%, median PFS of 16.7 months, and median OS of 27.6 months.[25] Currently there were no randomized clinical trial that directly compared these second-line ALK inhibitor treatments.

Other new ALK inhibitors which had been developed and currently under investigations in many clinical trials include Entrectinib (RXDX-101, NMS-E628, Ignyta), Lorlatinib (PF-06463922, Pfizer), TSR-011 (Tesaro), ASP3026 (Astellas Pharma), X-376 and X-396 (Xcovery), CEP-28122 and CEP-37440 (Teva).[26] The third-generation inhibitor Lorlatinib, selectively active against ALK and ROS1, harbors impressive biological potency; it has sub-nanomolar activity against EML4-ALK enzymes and almost all its mutant forms, including the ones that drive resistance to Ceritinib and Alectinib.[12] It also has the potential of resensitization to Crizotinib.[27] Entrectinib, which active against NTRK1-3 and ROS1, has been reported to act against ALK-positive NSCLC too.[28] Such availability provides incomparable opportunities for the treatment of ALKrearranged NSCLC patients.

TREATMENT STRATEGIES

ALK-positive NSCLC are associated with a relevant incidence of CNS metastases, affecting approximately 35-50% of patients. It is not known whether ALK-positive patients have an increased risk of developing CNS metastases as an expression of the natural disease course or if this higher risk may be related to treatment with ALK inhibitors. While it is the first compound that active against ALK-positive NSCLC, Crizotinib inefficiently able to cross the blood brain barrier leading to a limited drug concentration in the cerebrospinal fluid.[29] CNS involvementresulted the first site of progression in 46% of ALK-positivepatients treated with crizotinib, with 85% of these lackingsystemic progression. Second generation ALK inhibitors such as ceritinib, and alectinib seems to outweigh the activity of crizotinib against CNS metastases.[10]

Subsequent use of ALK inhibitors may clinically benefit patients progressing on an initial ALK inhibitor. Crizotinib led sequences have a broader evidence base and more mature clinical outcomes than second-generation-led sequences. No evidence was found directly comparing different ALK inhibitor sequences.[30] Based on those several clinical comparisons of ALK inhibitor sequences and the available safety data, the National Comprehensive Cancer Network® (NCCN)[31] have released clinical practice guideline that can be used as a strategy in managing ALK-positive NSCLC as follows:

NCCN guideline put all first- and second-generation ALK inhibitors as the initial compound of choice in ALK-positive NSCLC. Although second-generation ALK-inhibitors had been compared to and showed some advantages to Crizotinib as front-line treatment for ALK-positive NSCLC in many clinical trials, the current standard first-line therapy for these patients is Crizotinib.[31]Some time during the clinical course of the disease, many patients will eventually develop resistance to Crizotinib. As have been mentioned previously, CNS involvement is the first site of progression in 46% of ALK-positive patients treated with Crizotinib.[32] If the patient had CNS progression on Crizotinib, radiotherapy to cerebral sitesof progression in association with Crizotinib continuation,represents an accepted treatment strategy.[31] Althoughthere are no randomized studies available,

brain radiotherapy without Crizotinib withdrawal in patients with isolated CNS progression give approximately 12 months prolongation, before furtherprogression occurred.[33] In patients with symptomatic isolated lesion systemic progression, definitive local therapy (eg, stereotactic ablative body radiotherapy or surgery) while continuing Crizotinib is recommended.[31]

The greatest promise in the treatment of ALK-positiveNSCLC patients with CNS involvement comes from second-generationALK inhibitors, such as Ceritinib, Alectinib, Brigatinib. All these new agents showed promising activityagainst CNS metastases, both in TKI-naive and inCrizotinib-progressing patients.However, the choice of second-generationALK inhibitors will be affected by identification of specific ALK resistance mutations.This paradigm incorporates repeat biopsies and decisionmaking based upon ALK resistance mutation status following disease progression either on first-generation, and later on, on second-generation ALK inhibitors.[34] If symptomatic disease progression (CNS or isolated systemic lesion) then occured on second-generation ALK inhibitors, the same recommendation to apply the definitive local therapy while continuing the ALK-inhibitorsthat are being used. If multiple systemic lesions develop, the next choice is to give the third-generation ALK-inhibitor Lorlatinib.[11,26,31] As also had been mentioned previously, in some patients who treated with Lorlatinib and become resistant to Lorlatinib, they might become re-sensitized to Crizotinib.[27]

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