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REVIEW

WHAT ARE THE UNCOMMON ANAPLASTIC LYMPHOMA KINASE (ALK) FUSIONS IN NON-SMALL CELL LUNG CANCER?

Dr Hind El Yacoubi [1], MD ; Dr Mohamed SOW [2], MD ; Pr Hassan ERRIHANI [1 2], MD PhD.

[1] Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco.

[2] Medical oncology department, National institute of oncology, Rabat, Morocco.

ABSTRACT

The lung cancer carcinogenesis is increasingly related to genetic disorders that lead to use specific targeted therapies which improve clinical outcome and survival. Gene fusion is one of the mechanisms of lung cancer pathogenesis besides gene mutation. The oncogenic echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene was the first described in non small cell lung cancer (NSCLC) and it's the most frequent ALK rearrangement, which occurs in approximately 5% of NSCLC. The development of sequencing technology has allowed the discovery of other ALK partners that cause an ALK fusion in NSCLC. They are still less known, however. The aim of this revue is to report the novel ALK fusions in NSCLC described in the literature and their particular characteristics. We will present the kinesin family member 5B (KIF5B) - ALK fusion, the huntingtin interacting protein 1 (HIP 1)- ALK fusion, and other uncommon ALK fusions.

KEY WORDS: ALK fusion, ALK partners, non-small cell lung cancer.

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Correspondence : Dr Hind El Yacoubi, Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco.
Email : drhind@hotmail.fr

INTRODUCTION

Nowadays, advanced researches in genetic abnormalities and targeted therapies have modified the strategy of cancer care worldwide. These findings are applied in lung cancer treatment that has changed from non-specific cytotoxic agents to specific targeted agents. Anaplastic lymphoma kinase (ALK) gene fusion positive in lung cancer is an example for personalized medicine in a subset of patients. It was first recognized in 2007 by the discovery of the oncogenic echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion gene in approximately 5% of non-small-cell lung cancer (NSCLC) cases [1]. EML4 is the most common ALK fusion partner described in NSCLC. Other ALK partners are less known, however. It could be a source of a false negative diagnosis of ALK fusion in NSCLC that has a therapeutic implication. The confirmation of an ALK positive fusion in NSCLC leads to use specific ALK inhibitors that improve clinical outcome [2]. Thus, the determination of uncommon ALK partners may enhance prognosis for this patient's subset. The aim of this review is to collect uncommon ALK fusion in NSCLC to help for a better care of these particular cases.

THE KINESIN FAMILY MEMBER 5B (KIF5B) - ALK fusion

KIF5B-ALK fusion is the most frequent after EML4-ALK in NSCLC [3-7]. It accounts for 0,42%-0,50% of the reported cohorts [3-4]. It consists of a gene rearrangement including portions of the KIF5B gene, which is located on the short arm of human chromosome

10, and the ALK gene located on the short arm of human chromosome 2, in NSCLC cells [3]. Many fusion variants were reported indicating distinct breakpoints and fusion points within KIF5B and ALK gene [3-7]. These fusions occur mainly between exon 20 of ALK gene and three exon of KIF5B gene: exon 24 [3], exon 15 [4], and exon 17 [6]. Each of these KIF5B-ALK fusion genes would be expected to produce a functional protein tyrosine kinase that has a transforming potential, confirmed in an in vivo tumorogenicity assay [3]. In addition, KIF5B-ALK fusion activates survival signaling, strengthens cell proliferation, and improves cell migration and invasion [4]. The histopathology is predominated by adenocarcinoma [3,4,5,7] with papillary pattern [3,5]. Although, other histological type are reported, like adenosquamous carcinoma [6]. The pattern of immunohistochemistry (IHC) staining of KIF5B-ALK fusion is diffuse and cytoplasmic in some cases [3-4], however, some cells showed an unequal staining profile with a perinuclear halo [3]. The fluorescence in situ hybridization (FISH) analysis confirmed the presence of a translocation t(2;10)(p23;p11) responsible for the generation of KIF5B-ALK fusion [3]. The identification of KIF5B-ALK fusion variants was confirmed using polymerase chain reaction (PCR) -based direct sequencing and/or reverse transcription polymerase chain reaction (RT-PCR) [3-7]. Clinically, the small number of cases reported doesn't allow concluding on specific clinical features for KIF5B-ALK rearrangement in NSCLC. It could occur in both men and women, two cases of three had a smoking history, two were stage IA and one was stage IV [4,5,7]. Both stage IA cases had surgery [4-5], with a locoregional and distant recurrence in one case [4]. Although, ALK inhibitors were not used in the reported cases to evaluate their efficacy to treat NSCLC with positive KIF5B-ALK fusion, they could be functional in this uncommon fusion because both KIF5B-ALK and EML4-ALK contain the tyrosine kinase domain of ALK which is the target of ALK inhibitors [8].

THE HUNTINGTIN INTERACTING PROTEIN 1 (HIP 1)- ALK fusion

Three variants of HIP 1- ALK fusion in NSCLC were reported in the literature [9-11]. They occured between exon 20 of chromosome 2 and distinct fusion point of HIP 1 gene in chromosome 7: exon 21 [9], exon 28 [10], and exon 30 [11]. HIP 1-ALK fusion allows the production of a fusion protein that comprises the coiled-coil domain of HIP 1 and the juxtamembrane intracellular region of ALK [9-10], thus the ALK tyrosine kinase activity may be activated aberrantly facilitating oncogenesis in the lung [9]. Two cases were adenocarcinoma [9,11] and one case was a squamous cell carcinoma [10]. Clinically, two patients were women never smoker [9,11], and the third case was a man with a smoking history [10]. Two patients had a surgical resection [9,10], followed by adjuvant crizotinib therapy in one case without any recurrence [9]. There was one stage IV that received crizotinib for 5 months and then progressed, a second line treatment with alectinib achieved a complete response before progressing after one year [11]. These findings suggest that ALK inhibitors require further investigation in this subset of patients.

AUTHORS' CONTRIBUTIONS

All the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

Other uncommon ALK fusion

Seven other ALK partners are reported in NSCLC suggesting the diversity of this gene fusion [12-18]. Togashi et al. described a case of kinesin-light chain 1(KLC1)- ALK fusion in a woman aged 47 years with an in situ lung adenocarcinoma, a FISH assay confirmed the presence of t(2,14)(p23;q32.3), and the nucleotide sequencing revealed a fusion between exon 9 of KLC1 and exon 20 of ALK [12]. In 2014, Choi et al reported a novel fusion of translocated promoter region (TPR) and ALK in a 60-year-old man ex-smoker with a poorly differenciated lung adenocarcinoma, RT-PCR revealed a fusion of TPR exon 15 to ALK exon 20, and the genomic PCR confirmed the chromosomal translocation:t(1;2)(q31.1;p23) [13]. Another ALK partner was described by shan et al in a woman aged 45 years ex-smoker, with a metastatic lung adenocarcinoma, ALK FISH was negative while IHC had a strong ALK expression, next generation sequencing revealed then a new ALK partner gene: baculoviral inhibition of apoptosis protein repeat containing six (BIRC6); the patient received crizotinib that achieved an objective response without progeression[14]. In 2016, Kim et al reported a novel SEC31A-ALK rearrangement between SEC31A exon 21 on human chromosome 4 and ALK exon 20 [14]. Histopatologically, it was a poorly differenciated lung adenocarcinoma with ALK FISH and IHC positive [15]. Gu et al described a particular case in a 69-year-old never smoker man who had an advanced lung adenocarcinoma harboring concomitant c-met overexpression, HER-2 amplification and a novel ALK fusion, namely spectrin beta non-erythrocitic 1(SPTBN1)-ALK fusion, which was created by an insertion between exon 6 of SPTBN1 gene and exon 20 of ALK gene [16]. Interestingly, the patient had an inherent resistance to crizotinib, chemotherapy, and radiotherapy with an overall survival of 8 months only; these data suggest that the coexistence of SPTBN1-ALK fusion, Met, and HER-2 may have been responsible for the failed response to treatment [16]. Two others ALK partners were reported tropomyosin-related kinase-fused gene (TFG) [17] and protein tyrosine phosphatase nonreceptor type 3 (PTPN3) [18], although the presence of TFG-ALK in lung cancer has not been proven with histopathological evidence [17]. The genetic structure analysis of PTPN3-ALK demonstred that exons 10 and 11 of ALK has been translocated between exons 2 and 3 of PTPN3, then the ALK kinase domain is absent in the produced fusion protein,thus,the PTPN3-ALK fusion may not respond to crizotinib [18,19]. The biological and clinical significance of these ALK partners in NSCLC requires further investigation because it seems that not all of the above mentioned ALK rearrangements respond to ALK inhibitors.

CONCLUSION

Targeting ALK fusion in NSCLC is a helpful way to promote the prognosis and survival. Thus, the ALK fusion diagnosis should be more specific and performing to identify even uncommon ALK partners by using new technologies. Their cost is higher to be prescribed routinely, though. Future studies are needed to define the patient profile that is more likely candidate to deep investigation to look for uncommon ALK fusion.

COMPETING INTERESTS

The authors declare no competing interests.

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