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ALK Rearrangement in Anaplastic Thyroid Carcinoma: A Discovery Towards a Personalized Approach?

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Anaplastic thyroid carcinoma (ATC) represents about 1% of all thyroid carcinomas [1]. ATC is the most aggressive form of thyroid carcinoma especially when metastatic - accounting for 14-50% of all thyroid cancer related deaths [2]. Prognosis and outcomes following local progression or metastasis are poor using conventional therapies - such as surgery, chemotherapy, and external beam radiation therapy - with only 20% survival at 1 year [3]. So far, previous attempts to use multi-target tyrosine kinase inhibitors have not improved survival outcomes [4]. Therefore, molecular screening for specific genetic alterations in ATC tumors may provide an opportunity for an efficient, targeted therapy.

In recent years, the discovery of a variety of molecular and genetic alterations in different malignancies leading to oncogenesis has provided an insight into the complexity of tumorigenesis. This information can be used to target specific markers with the objective of improving patient outcomes. Yoshihara et al. described potentially 'druggable' kinase fusions in 8.7% of thyroid carcinomas [5]. The anaplastic lymphoma kinase (ALK) TK receptor (TKR) has recently emerged as a potentially relevant biomarker and a therapeutic target in solid and hematologic tumors. The ALK TKR gene is located at 2p23.2 and belongs to the insulin receptor superfamily [6]. A variety of alterations in the ALK gene such as mutations, overexpression, amplification, translocations, or other structural rearrangements have been implicated in tumorigenesis [7]. Hamatani et al. reported that, in 10 out of 19 papillary thyroid cancer (PTC) cases, ALK rearrangements are involved in the development of radiation-induced adult-onset PTC [8]. Demeure et al. identified an EML4-ALK translocation as the driver of PTC [9].

We previously reported the identification of a recurrent Striatin-ALK (STRN-ALK) fusion - the result of a complex rearrangement involving the short arm of chromosome 2 - in thyroid carcinomas [10]. Kelly et al. showed that STRN-ALK fusion occurred with a higher prevalence in poorly-differentiated ATCs without other overlapping known driver mutations in these tumors [11]. These data demonstrate that STRN-ALK fusion occurs in a subset of patients with highly aggressive types of thyroid cancer and could be a potential therapeutic target in these patients

These recent reports also highlight the potential use of drugs such as crizotinib that target ALK rearrangement with proven efficiency in non-small cell lung carcinomas [12] for highly aggressive types of thyroid cancer. We previously described a remarkable response to crizotinib in a 71-year-old woman suffering from a chemoresistant ATC with lung metastases. Three months after the initiation of crizotinib, an exceptional response of more than 90% across all pulmonary lesions was observed [13]. The patient is still alive two years after the introduction of crizotinib. CT evaluation has shown a complete response and the treatment has been well tolerated without any grade 2 or higher adverse effect.

This encouraging outcome aside, the prevalence of ALK rearrangements in ATC and poorly-differentiated thyroid tumors still remains unknown emphasizing the need for such studies. Currently, a multi-institutional French study is evaluating the prevalence of ALK-rearrangements (ALK+) in ATC (Tuthyref network). At present, the methods to detect the different molecular alterations of ALK1 gene are limited to immunohistochemistry, fluorescence in situ hybridization (FISH) and reverse transcriptase PCR methods. Further efforts are warranted to determine the optimal, cost-effective method for routine diagnostic detection of ALK fusions in thyroid cancers.

In our previous case report, using FISH, an ALK rearrangement was identified in more than 50% of cells in the various components of the tumor (well-differentiated and ATC components as well as in a lung metastasis). Nevertheless, establishing the best percentage cut-off for ALK+ tumor cells, as determined by FISH, for deciding the introduction of a drug targeting ALK-rearrangement remains a challenge. Currently, a phase II multi-institutional study to evaluate crizonitib's efficacy in ATC ALK+ tumors is ongoing in France. Rare neoplasia with poor outcomes, such as ATC could be interesting to identify potential targets for new drugs based on molecular screening of gene alterations.

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