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AJT

LETTER TO THE EDITOR

Letter to the editor concerning "Liver transplantation for metastatic wild-type gastrointestinal stromal tumor in the era of molecular targeted therapies: Report of a first case"

To the Editor:

A case report by Iesari et al states that liver transplantation (LT) could be an effective treatment option for liver metastatic wild-type (WT) gastrointestinal stromal tumor (GIST).[1]

Although we find this therapeutic approach very challenging, we believe that this statement requires some clarifications due to the following observations.

It is widely known that KIT and platelet-derived growth factor receptor alpha (PDGFRA) genotyping alone is not sufficient for defining a WT GIST. Over the past few years, deeper molecular analyses have shown that KIT/PDGFRA WT GIST are a heterogeneous group of different entities rather than a single subtype of GIST.[2,3] In particular, the most recognized molecular subtypes of KIT/PDGFRA WT GIST are the following: SDH-*deficient* GIST, mainly characterized by SDHX (most frequently SDHA) mutations; RAS-pathway mutant GIST with NF1, BRAF or K-RAS mutations; GIST with fibroblast growth factor receptors (FGFR)-pathway deregulation; NTRK-positive GIST. Finally, KIT/PDGFRA WT GIST without these molecular alterations are called pan-WT GIST/all *negative* WT GIST (Figure 1).

These subtypes differ from each other not only in their molecular fingerprint but also in clinical behavior and overall prognosis. Several studies have suggested that SDH-*deficient* GIST primarily affects young women and gastric and multifocal primary localization, indolent metastatic tumors, and frequent involvement of lymph- nodes are some of the main characteristic features seen in this subset of patients.[3,4] On the other hand, BRAF KIT/PDGFRA WT GIST primarily arise from the small bowel and can present a more aggressive course.

The clinical features of the present case report of a female patient with a metastatic gastric GIST, disease -free for 4 years since LT, are identical to those seen in SDH-*deficient* GIST. A recent report by Benítez et al describes a similar case of a female patient with a metastatic GIST, called KIT/PDGFRA WT, disease free for 42 months after LT from a living donor.[5]

The identification of molecular events involved in the disease, such as the FGFR pathway deregulation, NTRK-gene fusions, or BRAF mutations, could be helpful for development of novel targeted molecular therapies for KIT/PDGFRA WT GIST, which are resistant to standard tyrosine-kinase inhibitors (TKIs).

In conclusion, we believe that it is necessary to reassess the designation of KIT/PDGFRA WT GIST and make sure that each clinical case of KIT/PDGFRA WT GIST is not without the comprehensive molecular characterization. Therefore, LT could be an effective treatment option for liver metastatic SDH-*deficient* GIST, as it is most suitable for the treatment of indolent tumors, like this molecular subset of GIST.

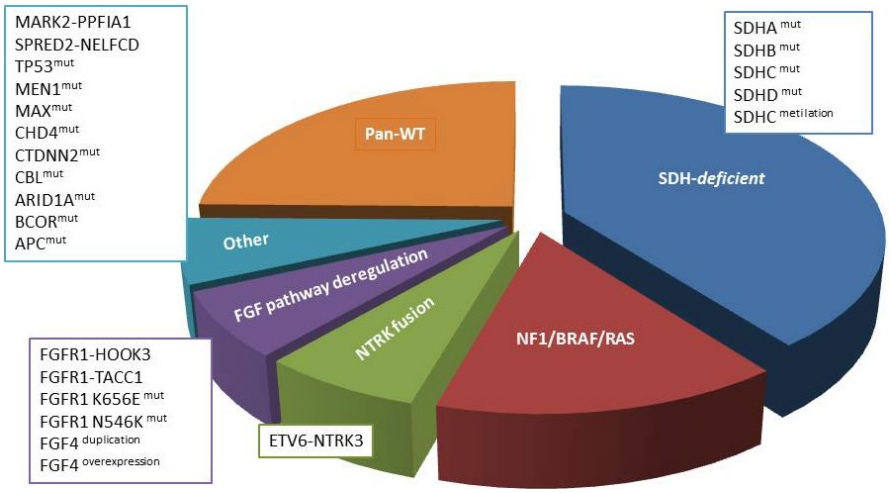

FIGURE 1 KIT/PDGFRA WT GIST in 2020

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

KEYWORDS

editorial/personal viewpoint, hematology/oncology, cancer/malignancy/neoplasia: metastatic disease, molecular biology

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