Genome Medicine

RESEARCH Open Access

Clinical and molecular characterization of *HER2* amplified-pancreatic cancer

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Abstract

Background: Pancreatic cancer is one of the most lethal and molecularly diverse malignancies. Repurposing of therapeutics that target specific molecular mechanisms in different disease types offers potential for rapid improvements in outcome. Although *HER2* amplification occurs in pancreatic cancer, it is inadequately characterized to exploit the potential of anti-*HER2* therapies.

Methods: *HER2* amplification was detected and further analyzed using multiple genomic sequencing approaches. Standardized reference laboratory assays defined *HER2* amplification in a large cohort of patients (n = 469) with pancreatic ductal adenocarcinoma (PDAC).

Results: An amplified inversion event (1 MB) was identified at the *HER2* locus in a patient with PDAC. Using standardized laboratory assays, we established diagnostic criteria for *HER2* amplification in PDAC, and observed a prevalence of 2%. Clinically, *HER2*- amplified PDAC was characterized by a lack of liver metastases, and a preponderance of lung and brain metastases. Excluding breast and gastric cancer, the incidence of *HER2*-amplified cancers in the USA is >22,000 per annum.

Conclusions: *HER2* amplification occurs in 2% of PDAC, and has distinct features with implications for clinical practice. The molecular heterogeneity of PDAC implies that even an incidence of 2% represents an attractive target for anti-*HER2* therapies, as options for PDAC are limited. Recruiting patients based on *HER2* amplification, rather than organ of origin, could make trials of anti-HER2 therapies feasible in less common cancer types.

Background

Pancreatic cancer is the fourth leading cause of cancer death in western societies, with a 5-year survival rate of less than 5% [1]. Systemic therapies are only modestly effective; however, there is emerging evidence that small groups of patients may respond well to specific treatments [2,3]. Current therapeutic development is focused on targeting molecular mechanisms, and this has resulted in significant improvements in outcome for several cancer types (for example, crizotinib for *EML4-ALK* fusion-positive non-small cell lung cancer (NSCLC)). This approach is shifting the traditional organ-based classification of cancer towards a new molecular taxonomy, and creating opportunities to apply therapeutics for the treatment of cancers originating in other organs that harbour similar molecular anomalies. Such indications for extension of existing therapeutics is attractive; however, specific molecular phenotypes and diagnostic characteristics are complex and usually inadequately defined [4,5]. The target population for cancers of organs, apart from where the therapeutic strategy was initially developed, often occur at low frequency, further adding to the challenge.

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