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HER2 expression, gene amplification and chromosome 17 copy number in primary pancreatic adenocarcinoma, metastatic lymph node and metastasis

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Abstract

HER2 expression or gene amplification is crucial for performing targeted therapy. We assessed p185^{HER2} (p185) expression, HER2 amplification and copy number of chromosome 17 centromere (CEP17) in pancreatic adenocarcinoma (PAC). We analyzed 26 tumours at diagnosis, 21 metastatic lymph nodes (mLN) and 38 distant metastases (mTS) by immunohistochemistry and by FISH. p185 overexpression was shown in 4% of primary PAC, 6% of mLN and 29% of mTS. Amplification was found restricted to 10% of the mTS and increased CEP17 in 21% of mTS and 16% of mLN. Overexpression of p185 was present in all amplified cases but in only 36% of increased CEP17. In conclusion HER2 amplification and increased CEP17 were mainly related to mTS or mLN and increased CEP17 was not always linked to overexpression of p185.

Introduction

Pancreatic adenocarcinoma (PAC) remains an often incurable disease. The development of a new therapy with anti-p185^{HER2} monoclonal antibodies (Trastuzumab, Pertuzumab) [1] has been proposed although the status of HER2 gene in PAC and its correlation with clinical history remain not completely defined [1, 2].
In our study we evaluated the expression of p185, HER2 gene amplification and chromosome 17 centromere (CEP17) copy number in PAC. In addition, we compared p185 expression and HER2 gene status of primary PAC, metastatic matched lymph node (mLN) and unmatched distant metastasis (mTS).

Materials and Methods

We analyzed 26 tumours at initial diagnosis, 21 mLN, 38 mTS. We performed IHC, on paraffin-embedded tissues, using the PATHWAY kit by Benchmark XT system (Ventana). A score of 0 or 1+ was regarded as IHC negative and 2+ or 3+ as IHC positive. FISH was performed using the Pathvision® (Abbot) or ZytoLight kit (ZytoVision).

Results

p185 overexpression was shown in 3.8% of primary PAC, 5.8% of mLN and 28.9% of mTS. HER2 amplification was restricted to 10.5% of mTS, increased CEP17 was found in 21.5% of mTS and in 14.3% of mLN (tab. 1). In 3 cases, increased CEP17 was found in mLN and not in related primary PAC (fig. 1). p185 overexpression was found in 100% of amplified tumours *vs* 36.4% of tumours with increased CEP17 (tab. 2).

Tumour (number of cases)	p185^{HER2} Expression score (%)				Chr. 17 Aneuploidy	HER2 Amplification
	0	1+	2+	3+	Pos (%)	Pos (%)
primary tumours (n=26)	23 (88.4)	2 (7.8)	1 (3.8)	0	0 (0.0)	0 (0.0)
Lymph node (n=21)	20 (95.2)	0 (0.0)	1 (5.8)	0	3 (14.3)	0 (0.0)
Metastasis (n=38)	24 (63.1)	3 (7.9)	11 (28.9)	0	8(21.5)	4 (10.5)
Total (n°=85)	67 (78.8)	5 (5.9)	13 (15.3)	0	11 (12.9)	4 (4.7)

Table 1. HER2 status in pancreatic ductal adenocarcinoma

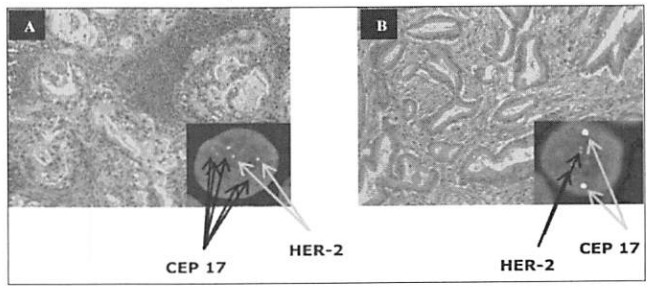

Figure 1. One of three cases in which CEP 17 amplification was seen in infiltrated lymphnode (A) but not in primary related tumour (B). HE: haematoxylin/eosin (20X); FISH: fluorescence in situ hybridization (100X).

Gene Status	P185 ^{HER2} expression score pos. (%)			
	0	1+	2+	3+
Disomy (n=70)	58 (82.9)	5 (7.1)	5 (7.1)	0 (0.0)
Aneuploidy (n= 11)	7 (6.4)	0 (0.0)	4 (36.4)	0 (0.0)
Amplification (n=4)	0 (0.0)	0 (0.0)	4 (100%)	0 (0.0)

Table 2. Association between HER2 gene status and p185^{HER2}

Discussion

HER2 amplification and increased CEP17 were found more frequently in mTS and in mLN than in primary PAC suggesting the need for the pathologist to evaluate HER2 status in all three tissue samples, as this may cause different responses to HER2 targeted therapy. However, we found that increased CEP17 was not always related to p185 overexpression. The possible explanation of this phenomenon is that the expression was related to cellular activation.

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