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Case Report
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Excellent Response to Dual Her2 Targeted Therapy in a Patient with Advanced Colorectal Cancer in Fourth Line of Treatment

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Abstract

Men 47 years old with staged IV colon cancer Ras wild type and her 23+, who had progressed to all approved treatments, get an spectacular response with dual her2 targeted Therapy without chemotherapy. This is the first case reported with this treatment, supporting the results of HERACLES study, as well as encouraging the development of phase III studies.

Keywords: Colon cáncer; Her2; Trastuzumab; Lapatinib

Introduction

Her2 neuis an important oncogen in breast and gastric cancer, but its prevalence and significance in Colorectal cancer (CRC) is poorly documented.

Any studies have shown her2 overexpression rates so low (3.8%), at least in therapeutic ranges (2+ o 3+ for IHC), than have not justified the developement of this marker to therapeutic management of Colorectal cancer [1].

Case Presentation

Male 45 years old, with unique history of hypertension well controlled.

He was diagnosed on January 2014 of a sigma adenocarcinoma stage IV, with liver metastases. Valued in multidisciplanary committe, with asymptomatic primary and irresecab leliver metastasis, began systemic treatment with palliative chemotherapy (Figure 1A and B).

He Received first line treatment into clinical trial VISNU [2] after molecular study (native Ras, native PI3K, native Braf and 10 circulating tumor cells), randomized to FOLFOX-BEVACIZUMAB. After 17 cicles, with best response of partial response after 6 cicles, we stopped treatment for disease progression in november 2014 (Figure 2A and B). We changed treatment to FOLFIRI-CETUXIMAB, begining on 24.11.14, with best response of partial response documented in first reevaluation after sixth cicle, and suspending treatment due to progression after twelfth.

On june 2015, began third line treatment with regorafenib, with liver progresion in first reevaluation on september 2015.

The Patient maintained Excellent overall status, but needed morfine for abdominal pain and in october began with tumoral fever controlled with anti-inflamatory (naproxene).

On december 2015, with demonstrated her2 overexpression (IHC 3+), and supported for results of HERACLES study presented in ASCO 2015 [3], the Patient began treatment with dual her2 targeted therapy. Received trastuzumab 2mg/kg (first dose 4mg/kg) and lapatinib 1000mg/day. The Patient had excellent tolerance, with trombopenia G2 at the beginning, resolved with one week break, and rash grade 1. The Patient had significative clinical benefit, stopping naproxene and morphine, and with analytic and radiologic response after third and sixth cicle of treatment.

In june 2016, Patient began with pruritus secondary to colestasis, confirming tumoral progression in TC-scan, with a progression free survival of 6 months. The Patient died in august 2016 (Figure 3A and B).

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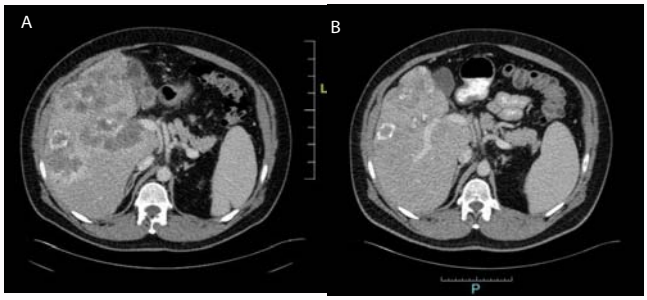

Figure 1a: (December 2015 TC scan).
Figure 1b: (April 2016 TC scan).

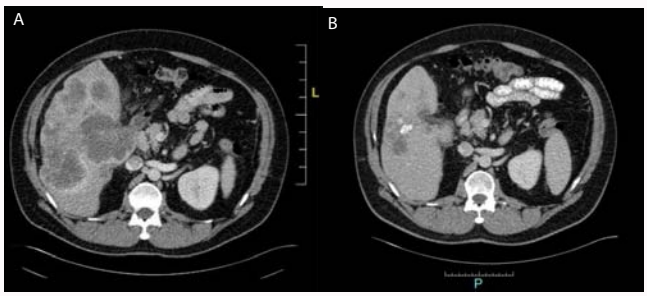

Figure 2a: (December 2015 TC scan).
Figure 2b: (April 2016 TC scan).

Discussion

Use of Her2-targeted therapy added to standard chemotherapy forme tastatic colorectal cáncer, was failed in two clinicaltrials, due to lack of efficacy [4] or insufficient accrual [5].

More recent studies have shown, nevertheless, higher over expression rates, until 10%, confirming this overexpression, both in the primary tumor and the metastasis (suggesting that overexpression is an early molecular alteration that persist during tumour progression). It is documented her2 over expression independent to kras status, finding her2 overexpression in therapeutic range in 5.3% of patients with mutated kras and 7.5% of patients with native kras [6].

Pre clinical studies show her2 overexpression in 7% of colorectal patients, further showing in cancer patients-derived xenografts that HER2 activating mutations in to colorectalcancer celllines produced resistance to anti-EGFR therapy by sustaining MAPK phosphorylation. In this study, treatment with a single HER2 targeted drug (trastuzumab, neratinib, orlapatinib) delayed tumor growth, but dual HER2 targeted therapy with trastuzumab plus tyrosine kinase inhibitors produced regression of these HER2 mutated PDX's [7].

On this basis, it was designed HERACLES study [8], with two investigation alarms: trastuzumab + lapatinib (Arm A) and Trastuzumab + Pertuzumab (arm B, pending results).

The arm A results were presented in ASCO 2015. Patients progressing after fluoropyrimidines, oxaliplatin, irinotecan, cetuximab or panitumumab were eligible if tumor was HER2+ [IHC3+ or 2+ and FISH positive (HER2:CEP17 >2) in > 50% cells and kraswt. It is allowed previous treatment with bevacizumab, aflibercept or regorafenib. All patients receive-lapatinib 1000 mg daily and trastuzumab 4 mg/kg iv load, followed by 2 mg/kg iv weekly

Primary end point was Objective Response Rate according to

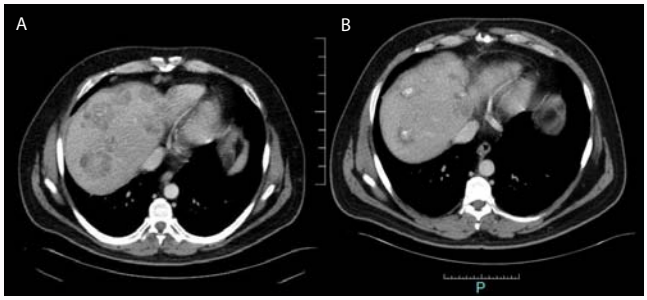

Figure 3a: (December 2015 TC scan).
Figure 3b: (April 2016 TC scan).

Table 1: Her2 targeted therapy in CCR cancer.

Analiticchanges	November 2015	April 2016
GOT/GPT (UI/l)	72/42	39/39
FA/GGT (UI/l)	450/283	163/184
CEA (ng/ml)	800	131
Ca 19.9 (UI/ml)	204	21.3

RECIST 1.1 criteria. Secondary end points are description of the frequency and severity of Adverse Events and PFS.

From 849 patients with mCRC KRAS exon 2 wild-type patients, 46 (5.4%) were HER2-positive. 24 patients were enrolled but 23 were evaluable for response. 18 patients had HER2 IHC 3+ tumours and 6 patients had HER2 IHC 2+ tumours. In 83% of patients, the primary site of tumour was left colon. Median number of prior lines of therapy was 5 (range 2-8) with 83% of patients who received more than 3 prior therapy regimens. All patients were treated previously with cetuximab or panitumumab. How ever, previous response to EGFR monoclonal antibodies was 0%.

The study treatment was well tolerated, with no grade 4-5 toxicities. The compliance was good with 96,4% of dosage received as planned. There was no patient off-treatment due to toxicities.

The primary endpoint was met with 8 out of 23 objective responses in patients heavily pretreated with standard therapies. The response rate (partial response plus complete response) was 34,7%. Stable disease of at least 4 months was recorded in 30,4% of patients. The disease control rate was 78%.

Median TTP was 5,5 months. The TTP by HER2 score was 7,3 months in patients with HER2 3+ and 4,2 months in HER2 2+.

The response and tolerance obtained in our case, according to results of phase II trial HERACLES, encourage to continue with the development of her2 targeted therapy in CCR cancer (Table 1). Probablyits use in early lines of treatment could improve these results, justified fortheaparent anti-EGFR resistence observed in preclinical studies [7] and HERACLES trial [8].

Besides, the Won-Sukstudy motivate the her2 analysis in CCR independently of RAS mutation [6].

If we consider that at least5% of patients may have an Her2 overexpression, according to CCR prevalence, it would be a therapeutic option to approximately 60000patientseveryyear, higher than the number of patients who may benefit From other targeted treatments like ALK inhibitors in lung cancer.

The drugs optimization, specially targeted treatments, with a

known predictive marker, is critical. The optimal cancer treatment goes in the way to selection treatment according to molecular markers rather than anatomic or clinical features.

Declaration of interests the authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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