Case Report

Colorectal Cancer

Prolonged response of widely metastatic HER2-positive colon cancer to trastuzumab therapy

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Emerging evidence suggests a small subset of late-stage colon cancer driven by HER2, a biomarker routinely evaluated in select breast and gastric cancers, may respond to HER2-targeted therapy. Herein, we describe a 49-year-old male with widely metastatic colon cancer originating in the sigmoid colon. After failing standard therapy, a biopsy specimen of the tumor was evaluated for novel biomarkers using molecular profiling. After identification of *ERBB2* (HER2) amplification using *in situ* hybridization, the patient subsequently received a trial of trastuzumab monotherapy and experienced a dramatic and durable response. This report builds on our understanding of using precision oncology to improve survival in metastatic colon cancer.

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Case report

A 49-year-old white male presented on August 2002 with asymptomatic, heme-positive stools; further work-up culminated in a sigmoid colectomy later that month. Pathology revealed a moderately differentiated adenocarcinoma in the sigmoid colon with metastasis in 6 of 20 pericolonic lymph nodes (T3b N2 M0 G2). He was subsequently assigned to the C-07 NSABP protocol's control arm, receiving 5-FU and leucovorin.

The patient was asymptomatic when he experienced a rise in his carcinoembryonic antigen (CEA) in 2005; a subsequent work-up led to resection of a solitary hepatic met (11/2005) and adjuvant FOLFIRI plus bevacizumab (February 2006). Bevacizumab was prematurely terminated after 2 months secondary to a pulmonary embolus. Upon completion of FOLFIRI (07/2006), he demonstrated no evidence of disease and an unremarkable CEA (2 ng/ml). Later, though, rising CEA values led to solitary pulmonary nodule finding by computed tomography (CT). This culminated in a pulmonary nodulectomy (6/2007), with pathology showing a metastatic colon adenocarcinoma recurrence. Recurrent nodularity in both the lungs and liver were found in latter half of 2007 and April 2008, respectively, all treated using radiofrequency ablation (RFA).

On July 2008, the patient presented with a bowel obstruction secondary to a large tumor burden within the pelvis. Disseminated cancer throughout the pelvis and pelvic sidewall effectively precluded a debulking option. The patient instead underwent multiple tumor biopsies and clip placements at sites of greatest tumor burden for potential guidance of palliative radiation therapy. A diverting colostomy was also performed. Besides routine pathology, one biopsy specimen was submitted to Caris Life Sciences (Phoenix, AZ) for molecular profiling, revealing a HER2 immunohistochemistry (IHC) membranous staining intensity of 2+ in 80% of tumor cells using an internal consensus interpretation based on breast cancer guidelines and emerging evidence in gastric and gastroesophageal cancer. The specimen was sent to an outside lab for *ERBB2* (HER2) FISH testing and confirmation, showing an *ERBB2* amplification ratio (HER2/CEP17) of 7.1. Besides EGFR expression, other molecular profiling tests were unremarkable.

Future Medicine

Table 1. IHC expression in colon and rectal cancer.

Study (year)	Patients (n)	Antibody	Interpretation	Results (Percent Expression)	Ref.
Edenfield (2014)	4110	4B5 clone monoclonal antibody (Ventana, AZ, USA)	Membranous staining only	1.8% (81/4110)	[8]
Ghaffarzadegan (2006)	69	Hercep-Test (Dako, Denmark)	Cytoplasmic and membranous	59.4% (41/69)	[5]
Heppner (2014)	1645	SP3 clone monoclonal antibody (Thermo Fisher, CA, USA)	Membranous staining only	1.6% (9/1645)	[9]
Schuell (2006)	77	Hercep-Test (Dako, Denmark)	Membranous staining only	2.6% (2/77)	[4]

After discussing options in the setting of *ERBB2* amplification and a CEA of 12.4, a trial of palliative trastuzumab (1 mg/kg/week) was initiated. The patient experienced a greater than 50% CEA reduction within 6 weeks and complete normalization of his CEA (1.9 ng/ml) by January 2009. A trial of adjuvant irinotecan at 180 mg/m^2 in December 2008 was tried but aborted after three doses by patient request.

With normalization of his CEA, a follow-up CT was conducted in January 2009, revealing no pelvic masses. Surgery for reanastomosis was then undertaken in March 2009. Surgical findings revealed no disease at the sites of previously implanted clips, no peritoneal disease and extensive necrosis of a resected hepatic nodule.

Over the ensuing 3.5 years, the patient experienced only intermittent, modest elevations of CEA, one time culminating in RFA and cryoablation of a right lung nodularity followed by immediate normalization of CEA. A slow, asymptomatic rise of his CEA once in 2012 was associated with a radiologic finding in the right lung of tumor versus postoperative treatment pneumonitis. Throughout, trastuzumab was administered but had to be discontinued in November 2012 secondary to highly symptomatic congestive heart failure.

Off trastuzumab, the patient developed a rapid rise in CEA. Subsequent panitumumab and regorafenib yielded only transient responses, with both discontinued secondary to toxicity. With further progressive disease in the pelvis detected on August 2013, a repeat biopsy with molecular profiling by Caris Life Sciences was performed. Findings demonstrated persistent *ERBB2* amplification by chromogenic *in situ* hybridization (CISH, ratio = 6.97) and HER2 IHC 3+ positive staining involving 90% of tumor cells. A brief course of capecitabine monotherapy (between September 2013 and November 2013) was initiated, but this and the evolution of an enterovesical fistula led to the patient's subsequent death from refractory carcinoma of the colon.

Discussion

HER2-targeted therapy has revolutionized the management of HER2-positive breast cancer in both the adjuvant and metastatic settings. HER2 overexpression is uncommon in nonbreast, nongastric malignancies, but trastuzumab appears to be therapeutically agnostic when the appropriate target is present. HER2-positive subsets of gastroesophageal junction (GEJ) and gastric carcinoma are relevant examples with up to 10–20% of esophagogastric carcinomas overexpressing HER2 [1,2]. In the Phase III ToGa trial randomizing between cisplatin plus fluoropyrimidines plus/minus trastuzumab, both objective response rate and median overall survival favored the trastuzumab arm [3].

The actual incidence and significance of HER2 expression remains controversial outside of breast and gastric cancers. Schuell and colleagues evaluated 77 surgically resected specimens and reported 70% negativity for HER2 expression, weak immunostaining in 27% and strong expression in only 3% [4]. They concluded HER2 targeting would not likely play a role in the management of colorectal cancer. By contrast, Ghaffarzadegan *et al.* studied 69 paraffin-embedded colon cancer specimens for HER2 expression and reported an exceptional 60% positivity and 40% negativity, and postulated potential clinical utility of HER2-directed therapies [5]. The prognostic significance of HER2 expression in locally advanced rectal cancer was reported with higher HER2 expression correlating with a significant survival benefit compared with low expression [6]. In all, 28.7% of the resected specimens were scored as positive. Uncertainty surrounds the reports of divergent membranous versus cytoplasmic overexpression and underscores the lack of correlative clinical data, and the wide variation in reported HER2 positivity is likely a consequence of assay technique, not diversity of colorectal carcinoma biology [7] (Table 1). Future trials will, hopefully, elucidate and optimize evaluation of HER2 (*ERBB2*) in colon cancer.

Our group found a rate of 1.8% overexpression from a database of more than 4000 patients interrogated with multiplatform testing, including gene sequencing, IHC and gene amplification [8]. Heppner *et al.* reported similar findings with 1.6% positivity of primary colorectal carcinomas as HER2 positive [9].

While clinically meaningful HER2 overexpression/*ERBB2* amplification is uncommon, this case report underscores the potential utility of trastuzumab monotherapy alone to produce a very prolonged and clinically meaningful response in a minority of patients. Targeting small subsets of molecularly and genomically defined patients is now quite common in a variety of other malignancies, most notably adenocarcinoma of the lung [10]. With further study, colon cancer management could adopt this approach.

Besides monotherapy, combination HER2-targeted therapy in colon cancer may also be a consideration. As of this writing, prospective clinical data are limited to the HERACLES trial, which enrolled patients with HER2 positive disease (as defined by an IHC of 3+ or IH2 2+ with FISH positivity and greater than 50% of cells) with metastatic, KRAS wildtype colorectal cancer resistant to standard therapies. After initial presentation at ASCO Annual, HERACLES was later updated and published with 27 evaluable patients achieving 1 complete response (CR, 4%), 7 partial response (PR, 26%) and 12 with stable disease (SD, 44%). Of note, the lone patient with a CR remained in remission for 144 weeks with trastuzumab plus lapatinib [11]. Along a similar vein, MyPathway, a Phase IIA study of selected targeted agents predicated on molecular profiles, was presented by Hainsworth and colleagues at ASCO 2016 [12]. They accrued 20 patients with colorectal carcinoma with HER2 amplification or overexpression. Results demonstrated 7 (35%) with CR + PR and 3 (15%) with SD of greater than 120 days for a clinical benefit rate of 50%. Siena *et al.* have opened the HERACLES-rescue trial utilizing T-DM1 in the population as defined by the HERACLES trial but progressing despite trastuzumab and lapatinib treatment. This trial has been initiated following preclinical investigation of patient-derived xenografts generated from the acquired resistant patient population wherein T-DM1-treated animals demonstrated response [13].

Recently, Parikh and colleagues reported the use of trastuzumab-DM1 as a third-line treatment with a seven month radiographic disease control until progression followed by three months of disease control with trastuzumab and pertuzumab combination therapy [14]. Another case report, by Diel *et al.*, described a patient who progressed on CAPOX but responded to treatment with the addition of trastuzumab [15]. Our case is unique in the 4-year duration of favorable disease control and the termination of therapy secondary to toxicity, not disease progression. This underscores the potential for dramatic, long-term disease control with extremely well-tolerated monotherapy in a subset of patients. This report, coupled with the aforementioned studies, should elevate discussion around routine HER2 determination in patients with metastatic colorectal cancer. Larger trials, though, will be necessary to determine when HER2 testing should be performed in colon cancer.

Two emerging, HER2-related topics in colon cancer are sidedness and the role of *ERBB2* mutations in colon cancer. Various groups are now reporting molecular differences between right-sided and left-sided colon cancer [16]. In one study by Missiaglia and colleagues, both EGFR (i.e., HER1) and HER2, were more common in the distal than in the proximal colon (12.6% [16/127] vs 1.4% [1/72] [$p < 0.001$], respectively) [17]. The second topic of interest is *ERBB2* somatic alterations. A recent publication by Kavuri *et al.* indicates *ERBB2* could be a potential target in colon cancer [18]. More studies will be needed to determine the impact of sidedness and *ERBB2* in the management of colon cancer.

Our case study underscores the potential striking magnitude and duration of response in a heavily pretreated patient with massive tumor burden. Improved molecular predictors of response in HER2-overexpressing patients will potentially allow for progressive improvement in clinical benefit. While the molecularly defined subset of patients is small, the clinical significance in an individual patient may be marked and is well within the practice culture of medical oncologists identifying and managing subsets of adenocarcinoma of the lung. Further studies in a critically defined subset of patients wherein HER2-driven disease is identified and refined will be required to optimally manage these patients.

Financial & competing interests disclosure

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Summary points

- HER2 expression and gene amplification has been found in a variety of tumors, including gastrointestinal cancers such as colon cancer.
- Like EGFR, HER2 expression and amplification is more often found in left-sided colon cancers.
- Based on this case report and recent literature, a subset of colon cancer patients may derive clinical benefit from HER2-targeted therapy.
- Some patients may derive prolonged response with only trastuzumab monotherapy.
- Immunohistochemistry or *in situ* hybridization is a viable methodology for accessing HER2 in colon cancer.
- Molecular profiling may identify novel treatment options not previously considered in the late stage setting.
- Future clinical trials could be designed to assess which patients derive the most benefit from HER2-targeted therapy in colon cancer.
- Further studies are warranted to standardize HER2 testing in colon cancer.

Ethical conduct of research disclosure

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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