Case report

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Personalized therapy based on sequential molecular analysis leads to 30 months of survival in a patient with diffuse unresectable gastric linitis plastica

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Abstract

Introduction: Diffuse gastric cancer is associated with poor prognosis. We report a patient with metastatic gastric linitis plastica harboring human epidermal growth factor receptor 2 (*HER2*) activating mutation and *HER2* amplification.
Case description: The patient received 5-fluorouracil/folinic acid and oxaliplatin combined with trastuzumab/pertuzumab, resulting in disease control for 8 months. Second-line therapy with nivolumab and trastuzumab/pertuzumab was well-tolerated, with macroscopic peritoneal response. Following ovarian progression and surgical resection of ovarian metastases, immunohistochemistry of PD-L1 was negative; proteomics demonstrated normal expression of HER2 and absence of PD-L1, while genomics showed *HER2* amplification, suggesting mechanisms of escape to dual HER2 blockade by downregulation of HER2 and to nivolumab by the absence of PD-L1. Based upon this and nonexpression of biomarkers of taxane resistance, therapy was changed to paclitaxel. Two and a half years after diagnosis, the patient is undergoing treatment, with excellent performance status.
Conclusions: Molecular analysis and personalized therapy can help optimize treatment in difficult-to-treat cancers.

Keywords

Stomach, cancer, survival, trastuzumab

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Introduction

Diffuse gastric cancer is associated with poor survival outcomes. Recommended first-line chemotherapy includes a combination of platinum and fluorouracil with or without anthracycline. Routine *HER2* testing by immunohistochemistry (IHC) and/or fluorescence in situ hybridization is indicated to determine whether to add trastuzumab to a first-line combination chemotherapy regimen. Approximately 23% of gastric cancers overexpress HER2.[1] In the ToGA trial, the addition of trastuzumab to standard first-line chemotherapy for HER2-positive metastatic gastric cancer improved overall survival (OS) (13.3 months) as compared with chemotherapy alone (11.1 months), although diffuse-type cancers did not show an OS benefit.[2]

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Table 1. Official nomenclature of single nucleotide variants.

Gene	Description	cDNA nucleotide	Protein	Allelic frequency (WES/TGS)	gDNA nucleotide
SNV					
ERBB2	p.S310Y	NM_004448.3: c.929C>T	p.(Ser310Phe)	78%/76%	Chr17(GRCh37): g.37868208C>T
ERBB2	p.D582N	NM_004448.3: c.1744G>A	p.(Asp582Asn)	17%/nc	Chr17(GRCh37): g.37873579G>A
KMT2D	p.R5340Q	NM_003482.3: c.16019G>A	p.(Arg5340Gln)	11%/nc	Chr12(GRCh37): g.49418394C>T
SOX2	p.N24Rfs	NM_003106.3: c.70_89del	p.(Asn24Argfs*65)	13%/nc	Chr3(GRCh37):g. 181430218_181430237del
TP53	p.R273H	NM_000546.4: c.818G>A	p.(Arg273His)	11%/12%	Chr17(GRCh37): g.7577120C>T
Gene	Segment coordinate (GRCh37)	Copy number	Tumor mean depth	Normal mean depth	
CNV					
ERBB2	chr17:37821607-37900465	13,8	896 X	102X	
Gene 1	Gene 2	Segment coordinate (GRCh37)	Short karyotype		
Fusion transcript					
PGAP3		chr17:37856564-chr17:37830932	t(17,17) (q12,q12)		
ERBB2					

WES: whole exome sequencing; TGS: targeted gene sequencing; SNV: single nucleotide variant; CNV: copy number variation.

Case Report

We report the case of a 49-year-old woman with gastric linitis plastica and peritoneal carcinomatosis. At diagnosis, the patient underwent abdominal surgery for bowel obstruction. Peritoneal biopsies revealed poorly differentiated gastric adenocarcinoma with predominant signet ring cells. Endoscopy showed thickened gastric folds and biopsies confirmed the diagnosis of diffuse-type gastric cancer. PD-L1 expression assessed by IHC was observed in 5% of tumor cells and in 10% of immune cells. Targeted gene sequencing identified a *HER2* activating mutation p.S310F (70% allelic frequency), as well as *HER2* gene amplification with a mean copy number of 9.3.[3] IHC showed HER2 overexpression (score 3+). The patient had a poor performance status (PS3) with severe malnutrition, loss of >10% of initial body weight within a month, albumin level <20 g/L, bowel obstruction related to peritoneal carcinomatosis along with ureteral obstruction, and elevated creatinine due to extrinsic compression. Bilateral hydronephrosis was first managed with percutaneous bilateral nephrostomy, then replaced by double-J ureteral stents. Despite her general status, a multidisciplinary team selected FOLFOX (5-FU, folinic acid, and oxaliplatin) combined with trastuzumab and pertuzumab as first-line therapy, with stable disease as best response but indisputable clinical improvement (disappearance of the bowel obstruction, weight gain, return to normal albumin level, and recovery of an Eastern Cooperative Oncology Group performance status of 1). Oxaliplatin was discontinued after 6 cycles due to neurotoxicity, while 5-FU and anti-HER2 agents were continued as maintenance therapy. After 8 months of anti-HER2 targeting, the patient began compassionate use of the anti-programmed death receptor-1 (PD-1) monoclonal antibody nivolumab in combination with trastuzumab and pertuzumab with good tolerability. Computed tomography evaluation 3 months later revealed macroscopic peritoneal response, but progressive metastases in the ovaries. Resected ovarian metastases analyzed within the Molecular Screening for Cancer Treatment Optimization (MOSCATO) trial at Gustave Roussy Cancer Center (NCT01566019) revealed negative HER2 expression (IHC score 0), but *HER2* gene amplification and a *HER2* activating mutation in exon 8 (76% allelic frequency). Whole exome sequencing found a new *HER2* mutation p.D582N, as well as *KMT2D* and *SOX2* mutations, and *ERBB2-PGAP3* fusion (Table 1). Immunohistochemistry of PD-L1 revealed no expression of PD-L1 in tumor cells. Complementary proteomic analysis of the ovarian metastatic tissue by quantitative targeted mass spectrometry (NantOmics) confirmed the lack of HER2 overexpression and the absence of PD-L1 expression, suggesting that the resistant ovarian mass had escaped dual HER2 blockade by downregulation of HER2 protein and was unresponsive to nivolumab due to the absence of PD-L1 protein. Mutational load was 2.3 mutations per megabase (101

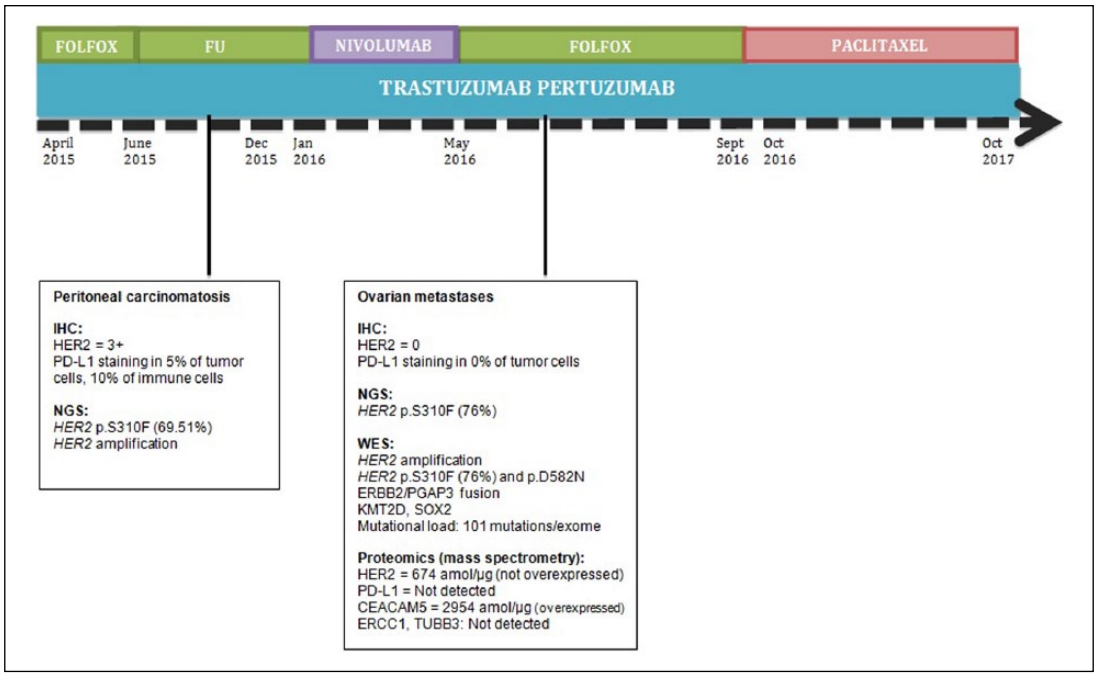

Figure 1. Treatment history and results of molecular analysis of tumor biopsy specimens from a patient with gastric linitis plastica.

mutations per covered exome), and PD-L1 expression by IHC was null. Proteomic analysis identified several potential therapeutic biomarkers, including lack of expression of class III β-tubulin, a biomarker of taxane resistance.[4] Based on these proteomic and genomic findings, weekly paclitaxel was selected (Figure 1) and targeted therapy with pertuzumab and trastuzumab was maintained. The patient has been stable for 1 year.

Conclusion

This report describes a dramatic improvement in general condition, a disappearance of bowel obstruction related to peritoneal carcinomatosis, and long-term survival in a case of severe metastatic diffuse-type gastric cancer treated by dual HER2 blockade in combination with chemotherapy. The rationale for dual HER2 blockade in gastric cancer is based on HER2-positive metastatic breast cancer, in which a combination of trastuzumab, pertuzumab, and docetaxel is the first-line treatment.[5] In HER2-positive metastatic breast cancer, a combination of trastuzumab, pertuzumab, and docetaxel improved OS compared with placebo, trastuzumab, and docetaxel. Clinical trials have yet to demonstrate dual targeting of HER2-positive gastric cancer with pertuzumab and trastuzumab; the phase III JACOB study is ongoing (NCT01774786). The use of nivolumab in this patient was based on the efficacy of nivolumab monotherapy in the CheckMate-032 trial of patients with advanced or metastatic gastric cancer; the objective response rate was 12% and median OS was 6.8 months (NCT01928394). The combined targeting of HER2 and PD-L1 is based on preclinical data. Tumor-infiltrating lymphocyte counts were higher in HER2-positive vs ER-positive/HER2-negative breast cancer. A clear correlation has been described between increase of lymphocytic infiltration and benefit from chemotherapy in *HER2*-positive breast cancer.[6] Combined targeting of HER2 and PD-L1 in HER2-positive transgenic mice decreased tumor size.[7] Clinical trials are currently evaluating the efficacy of anti-PD-1 antibody combined with anti-HER2 therapy in HER2-positive breast cancer (NCT02129556, NCT02605915, NCT02649686).

Genomic and proteomic analysis performed at diagnosis and upon disease progression pointed to a likely mechanism of acquired resistance. Indeed, HER2 protein downregulation by trastuzumab has been described in breast cancer cell lines overexpressing HER2 as well as in a patient with gastroesophageal cancer who also benefitted from sequential genomic and proteomic testing.[8] Resistance to PD-1 blockade is now the focus of intense research and hypotheses for tumor immune escape have been described.[9] Both preclinical and clinical data have demonstrated reduced upregulation of PD-L1 in response to interferon-γ in patients with melanoma resistant to pembrolizumab, thus indicating PD-L1 downregulation as a mechanism of escape to anti-PD-1 therapy.[10] The case described here demonstrates that patients with difficult-to-treat tumors may benefit from sequential molecular analysis to inform personalized treatment.

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Declaration of Conflicting Interest

The authors declare that they have no conflict of interest.
Fabiola Cecchi and Todd Hembrough are employees of NantOmics, where the proteomic analysis was performed.
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References

1. Gravalos C and Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008; 19: 1523–1529.
2. Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; 376: 687–697.
3. Kavuri SM, Jain N, Galimi F, et al. HER2 activating mutations are targets for colorectal cancer treatment. *Cancer Discov* 2015; 5: 832.
4. Kavallaris M, Kuo DY, Burkhart CA, et al. Taxol-resistant epithelial ovarian tumors are associated with altered expression of specific beta-tubulin isotypes. *J Clin Invest* 1997; 100: 1282–1293.
5. Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366: 109–119.
6. Loi S, Sirtaine N, Piette F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. *J Clin Oncol* 2013; 31: 860–867.
7. Stagg J, Loi S, Divisekera U, et al. Anti-ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti-PD-1 or anti-CD137 mAb therapy. *Proc Natl Acad Sci USA* 2011; 108: 7142–7147.
8. Sellappan S, Blackler A, Liao W-L, et al. Therapeutically induced changes in HER2, HER3, and EGFR protein expression for treatment guidance. *J Natl Compr Canc Netw* 2016; 14: 503–507.
9. Kim JM and Chen DS. Immune escape to PD-L1/PD-1 blockade: 7 steps to success (or failure). *Ann Oncol* 2016; 27: 1492–1504.
10. O'Donnell JS, Smyth MJ and Teng MWL. Acquired resistance to anti-PD1 therapy: checkmate to checkpoint blockade? Genome Med [Internet]. 2016 Oct 25 [cited 2016 Nov 22]; 8. Available at: ncbi.nlm.nih.gov/pmc/articles/PMC5080691/.