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CASE REPORT

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Dual HER2 blockade with lapatinib and trastuzumab in combination with chemotherapy in metastatic gastroesophageal adenocarcinoma

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Abstract

The development of resistance to trastuzumab in HER2-positive gastroesophageal cancer remains a problem. The use of dual HER2 blockade to overcome this is a therapeutic strategy that should be researched more extensively.

KEYWORDS

dual HER2, Gastroesophageal cancer, HER2, lapatinib, trastuzumab

1 | INTRODUCTION

Gastroesophageal cancers are one of the leading causes of cancer mortality globally. We report the case of a 64-year-old Chinese gentleman with HER2-amplified metastatic gastroesophageal junction adenocarcinoma, treated with dual HER2 blockade using lapatinib and trastuzumab in combination with chemotherapy. 14 months into treatment, he remains clinically well.

Gastroesophageal cancers are one of the leading causes of cancer-related mortality globally.[1,2] The prognosis is poor for patients with advanced disease. Median survival for patients with advanced disease on first-line chemotherapy is 12 months.[2,3] The human epidermal growth factor 2 (HER2) is amplified in approximately 15%-29% of patients with gastroesophageal cancer.[4] Trastuzumab combined with platinum/fluoropyrimidine-based chemotherapy is the standard first-line treatment for advanced, and HER2-positive gastroesophageal cancer following the ToGA (trastuzumab for gastric cancer) trial.[5] However, the development of resistance to trastuzumab remains a challenge for oncologists in improving the survival for these patients. After disease progression on first-line treatment, the role of further HER2 blockade is unclear. Dual combination of anti-HER2 agents with complementary mechanisms of action to target HER2 represents a promising therapeutic strategy. We report the case of a patient with metastatic, and HER2-positive gastroesophageal junction adenocarcinoma who was started on dual anti-HER2 therapy comprised of lapatinib and trastuzumab plus chemotherapy, following disease progression on trastuzumab and chemotherapy.

2 | CASE REPORT

A 60-year-old gentleman presented in November 2016 with complaints of dysphagia. He had no known comorbidities and was functionally fit with an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Investigations revealed a moderately differentiated adenocarcinoma of the gastric cardia invading the esophagus. Immunohistochemistry (IHC) studies revealed HER2 IHC

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3+, microsatellite stability, and programmed death-ligand 1 (PD-L1) combined positive score (CPS) score <1. A positron emission tomography-computed tomography (PET-CT) scan showed a hypermetabolic GOJ mass with two mediastinal lymph node metastases, staged cT3N1M0 (American Joint Committee on Cancer [AJCC], 8th edition).

He underwent neoadjuvant concurrent chemoradiotherapy, 41.4 Gy in 23 fractions over 4.5 weeks with 5 cycles of weekly carboplatin and paclitaxel, followed by radical esophagogastrectomy (Ivor Lewis approach) in February 2017. Postoperative histological staging was ypT2N0M0 indicating partial response. Resection margins were clear, and no lympho-vascular invasion was observed. 13 mediastinal nodes were removed, and none of which showed malignancy.

In November 2017, a PET-CT scan revealed metastatic relapse at the left lower lobe of lung and segment 7 of liver. Patient received eight cycles of CAPOX (capecitabine and oxaliplatin) and trastuzumab and achieved complete metabolic response. Six months later, PET-CT showed metastatic recurrence at the lung and liver. He was then rechallenged with six cycles of CAPOX and trastuzumab. After the fifth cycle, his tumor markers, CEA (carcinoembryonic antigen) and Ca19-9 (carbohydrate antigen 19-9) were gradually increasing. PET-CT showed mixed response with partial regression of the liver lesion but slightly larger lung lesion and a new FDG-avid lesion at the L2 vertebra (Figure 1A).

He was then referred to our institution for further management and was seen in July 2019. Upon our assessment, he was still maintaining a good performance status. He was started on lapatinib 1000 mg once a day (continuously), trastuzumab 6 mg/kg (day 1), and capecitabine 1000 mg/m^2 every 12 hours (day 1 to 14) of a 21-day cycle. This patient's liver function and renal profile were normal at baseline. Full blood count parameters were within acceptable range: hemoglobin 127 g/L (normal range: 130-170 g/L), white blood cell 3.8 × 10^9/L (normal range: 4-10 × 10^9/L), neutrophil count 2.37 × 10^9/L (normal range: 2-9 × 10^9/L), and platelet 128 × 10^9/L (normal range: 150-400 × 10^9/L). CEA and Ca19-9 prior to this treatment regime was 50.8 ng/mL (normal range: 0-2.5 ng/mL) and 84 U/mL (normal range: 0-33 U/mL), respectively.

Four months into treatment, PET-CT showed stable liver and left lower lobe lung lesions, but new hypermetabolic sclerotic lesions at the right femoral head and L2 and L4 vertebrae. His Ca19-9 was on a decreasing in trend, while serial CEA showed a gradual increase. Clinically, he was well and asymptomatic.

In view of oligometastatic disease, intensity-modulated radiation therapy (IMRT) was given to the L2 and L4 vertebrae (28 Gy/2#), right femoral head (24 Gy/2#), and the left lower lobe lung lesion (48 Gy/4#) for local control in February 2020.

A follow-up PET-CT in March 2020 showed reduced metabolic activity at the lung and bones, but a larger segment 7 liver lesion and hypermetabolic foci at C5 and C6 vertebrae (Figure 1B). He subsequently underwent radiofrequency ablation (RFA) of the segment 7 liver lesion. A biopsy of the liver lesion was done and confirmed sustained HER2 3 + expression.

This patient tolerated treatment well. Treatment-related toxicity was mainly Grade 1 hand-foot syndrome. He remained clinically well during the most recent review in September 2020. Left ventricular ejection fraction was maintained at 60% (he had a baseline ejection fraction of 66%; lower limit of normal: 55%). Fourteen months into treatment, his blood parameters were still within acceptable range. Total bilirubin and alkaline phosphatase were slightly elevated at 27 μmol/L (reference: <17 μmol/L) and 134 U/L (upper limit of normal: 129 U/L), respectively, while other liver function parameters were normal. Hemoglobin level was 96 g/L (normal range 130-170 g/L), white blood cell 2.9 × 10^9/L (normal range: 4-10 × 10^9/L), neutrophil count 1.74 × 10^9/L (normal range: 2-7 × 10^9/L), and platelet 145 × 10^9/L (normal range: 150-400 × 10^9/L). Renal profile remained normal. There were no significant hematological or biochemical impairment while on this treatment regime. A PET-CT done in September 2020 showed disease progression in the lungs and bone, with new liver and nodal metastases. At this point, CEA was 595.9 ng/mL (normal range: 0-2.5 ng/mL) and Ca19-9 was 1087 U/mL

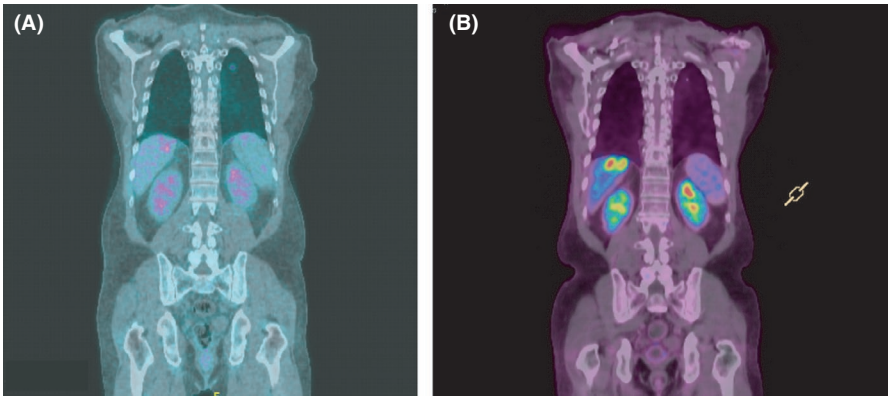

FIGURE 1 (A) PET-CT in July 2019; (B) PET-CT in March 2020. PET-CT, positron emission tomography-computed tomography

(normal range: 0-38 U/mL). He was counselled for a change in treatment regime and proceeded with RAMIRIS (ramucirumab and FOLFIRI).[6]

3 | DISCUSSION

HER2 amplification in gastroesophageal cancer is associated with poor prognosis and survival.[7,8] In the landmark ToGA trial, the addition of trastuzumab to doublet chemotherapy (cisplatin and fluoropyrimidine) in HER2-positive advanced gastroesophageal cancer showed significant improvement in progression-free survival (PFS) (6.7 vs 5.5 months, HR 0.71 (0.59 to 0.85), $P = .0002$) and overall survival (OS) (13.8 vs 11.1 months, HR 0.74 (0.60 to 0.91), $P = .0046$).[5] However, the marginal gain in median PFS raises a pertinent question as to whether the short-term PFS is attributed to resistance to Trastuzumab. Several mechanisms of resistance to trastuzumab have been identified, which include structural mutation of the HER2 receptor, hindering extracellular binding of trastuzumab to HER2, tumor heterogeneity in HER2 positivity and aberrant HER2 downstream signaling.[9] It highlights the challenge that oncologists face in improving the survival of patients with advanced gastroesophageal cancer.

The principle of dual HER2 blockade, which utilizes different HER2-targeted agents with complementary mechanisms to overcome drug resistance, has been researched and put into clinical practice in HER2-amplified breast cancer.[10,11] In the NeoALTTO trial, the combination of trastuzumab and lapatinib plus chemotherapy as neoadjuvant therapy significantly improved rates of pathological complete response in early breast cancer.[10] The ALTERNATIVE trial showed that dual HER2 blockade with lapatinib and trastuzumab plus an aromatase inhibitor had superior PFS benefit vs trastuzumab plus aromatase inhibitor (11 vs 5.6 months, HR 0.62 (0.45 to 0.88), $P = .0063$) in metastatic breast cancer.[11] The authors concluded that this combination offered a safe treatment regime for patients; its adverse events mainly Grade 1-2 diarrhea, rashes, nausea, and paronychia.[11]

The use of lapatinib and trastuzumab in HER2-amplified gastroesophageal cancer has only been investigated in isolation thus far. The TyTAN trial demonstrated superior objective response rate (ORR) in lapatinib plus paclitaxel vs paclitaxel (27% vs 9%; $P < .001$).[12] In the LOGIC trial, response rate was significantly higher in the lapatinib plus CAPOX arm vs placebo and CAPOX arm (53% vs 39%; $P = .0031$).[13] Hence, the combined use of these two anti-HER2 agents (lapatinib and trastuzumab) represents a novel approach in gastroesophageal cancer.

HER2 is one of the receptors in the epidermal growth factor receptor (EGFR) family. It requires formation of heterodimers with other EGFR family receptors, such as HER1 (EGFR), HER3, and HER4 for signal transduction of cellular proliferation and survival.[14] HER receptors are transmembrane glycoproteins that consist of an extracellular ligand-binding domain and an intracellular domain for tyrosine kinase activity.[15]

Trastuzumab is a monoclonal antibody against subdomain IV of the HER2 extracellular domain, which functions through various mechanisms including receptor degradation, inhibition of angiogenesis, and recruitment of immune cells resulting in antibody-dependent cellular toxicity[16] (Figure 2). Lapatinib is an oral, small molecule tyrosine kinase inhibitor that enhances HER2 inhibition by binding to the intracellular domains of HER1 (EGFR) and HER2, blocking autophosphorylation and downstream signaling[17] (Figure 2). In vitro and in vivo studies have demonstrated that lapatinib and trastuzumab interact synergistically to selectively inhibit HER2-amplified human gastroesophageal cells.[2,18] By targeting both the extracellular and intracellular HER2 domains, this represents a more complete HER2 blockade which hypothetically, may hinder drug resistance. This is an important subject that warrants further research as it broadens the treatment options available for HER2-positive advanced gastroesophageal cancer that has progressed on HER2 monotherapy.

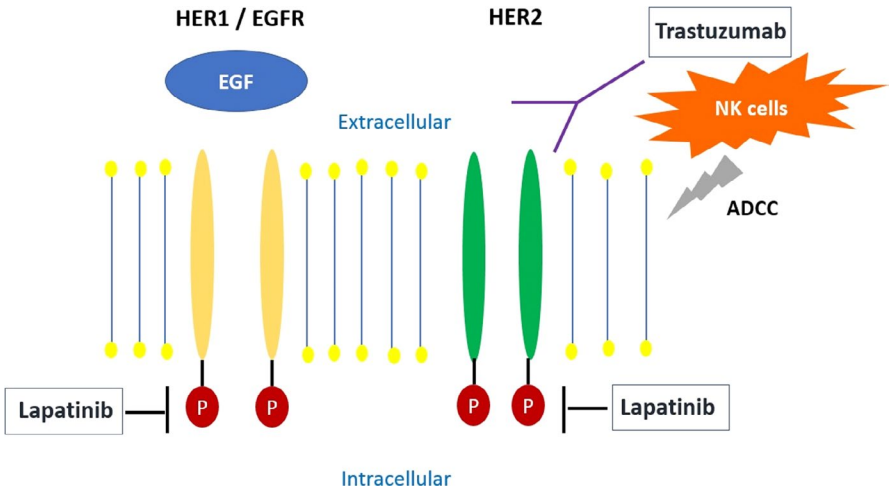

FIGURE 2 Schematic of a tumor cell with the mechanisms of action of HER-targeted therapies. ADCC, antibody-dependent cellular cytotoxicity; EGF, epithelial growth factor; NK, natural killer cell

In the case explained above, the patient's disease had progressed after being rechallenged with trastuzumab and CAPOX. He had received 14 cycles of trastuzumab and CAPOX in total, at the point of referral to our institution. The addition of lapatinib to trastuzumab was in tandem with the principle of dual HER2 blockade. The rationale for continuing trastuzumab in this case was based on a retrospective multicenter study, which showed significant improvement in median PFS and OS with the continued use of trastuzumab beyond progression (Median PFS, 4.4 vs 2.3 months, $P = .002$; OS, 12.6 vs 6.1 months, $P = .001$).[19] The OS and PFS benefits remained significant after accounting for ECOG performance status, number of metastatic sites, and measurable disease.

The patient was continued on capecitabine as a single chemotherapeutic agent in combination with lapatinib and trastuzumab. It is postulated that lapatinib may restore sensitivity to fluoropyrimidines in tumors that have ceased to respond to fluoropyrimidines, hence the decision to continue with capecitabine.[2] Although there was no significant OS benefit with the addition of lapatinib to CAPOX as first-line treatment of advanced HER2-positive gastroesophageal cancer, it was interesting to note that subgroup analyses showed prolonged OS in the lapatinib arm in Asian patients (16.5 vs 10.9 months, HR 0.68; [0.48 to 0.96], $P = .0261$) and in patients younger than 60 years of age (12.9 vs 9.0 months, HR 0.69 [0.51 to 0.94]; $P = .0141$).[13] This is applicable to our patient who is a Chinese Malaysian.

At the point of his disease progression, a biopsy of his liver lesion was taken and an IHC study to reconfirm HER2 status was requested. The rationale of this is based on findings from the T-ACT trial, which showed that 69% of patients in the study lost HER2 positivity at the point of disease progression on first-line trastuzumab-containing therapy.[20] Direct loss of HER2 amplification following trastuzumab-containing therapy highlights the importance for repeat biopsies to ascertain HER2 status following disease progression and may be the mechanism underlying resistance to anti-HER2 therapy.

This patient is in his fourteenth month of lapatinib, trastuzumab, and capecitabine. Despite the lack of objective response of the disease to treatment, this patient was asymptomatic during his gradual disease progression and maintained a good quality of life. He has reached longer than expected survival for the pathology of his disease.

4 | CONCLUSION

In conclusion, we believe that the use of dual HER2 blockade in combination with chemotherapy is a therapeutic strategy that should be researched more extensively in patients with HER2 amplified advanced gastroesophageal cancer.

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We would like to thank our patient who consented to have his case discussed for educational purpose. Published with written consent of the patient.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Dr E Von Cheong involved in conception of the work, drafting the work and revising the work critically for important intellectual content. Professor Gwo Fuang Ho involved in final approval of the version to be published, agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy, or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL APPROVAL

Ethics approval for this case report was waived by the University of Malaya Medical Centre Medical Research Ethics Committee (MREC) because it does not constitute research where it was conducted.

DATA AVAILABILITY STATEMENT

Data sharing was not applicable to this article as no data sets were generated or analyzed during the current study.

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