A CASE REPORT: HER2-TARGETED THERAPY IN COLORECTAL CANCER

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Abstracts

Colorectal cancer (CRC) is a malignant tumor arising from the inner lining of the colon or rectum and is the third most common cancer and the third leading cause of cancer-related deaths in the United States. Human epidermal growth factor receptor 2 (HER2) gene overexpressed or amplified CRC has shown treatment responses with HER2-targeted therapies. This article reports two cases of heavily pretreated metastatic CRC (mCRC) with HER2 overexpression who achieved a remarkable clinical response to trastuzumab plus pertuzumab.

Keywords: Human epidermal growth factor receptor 2 (HER2); Anti-HER2 therapy; Trastuzumab plus pertuzumab; Colorectal cancer.

INTRODUCTION

Colorectal cancer constitutes 10% of global cancer diagnoses and cancer-related deaths annually. At the time of diagnosis, 20% of patients have mCRC, with a 5-year survival rate of less than 20%. Recent advancements in genomic technology with large-scale molecular profiling of tumors have led to new treatment opportunities for these patients.

In approximately 2 - 5% of patients with CRC, overexpression or amplification of HER2 is observed, with a higher incidence in left-sided colon and primary rectal RAS/BRAF-wild-type (RAS/BRAFwt) tumors [1, 2, 3]. Currently, patients with left-sided RAS/BRAFwt tumors are treated with anti-EGFR therapy (i.e., panitumumab or cetuximab) with or without combination chemotherapy and/or anti-VEGF.

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However, accumulating evidence suggests that the presence of HER2 amplification or overexpression is associated with resistance to anti-EGFR therapy [4]. ERBB2 is a well-known oncogene that is successfully targeted in breast, gastric, and esophageal cancers. Recent reports indicate that patients with HER2-positive mCRC (HER2+mCRC) also benefit from anti-HER2 therapy. Despite promising data, targeted therapy for patients with HER2+mCRC is not available in Vietnam. This is mainly due to the challenges of obtaining regulatory approval based on single-arm studies in small subgroups of patients, such as those with HER2+mCRC. However, there is a clear unmet need for the availability of anti-HER2 agents as a standard treatment option for these patients. Therefore, this study aims to: *Report two HER2 overexpression CRC cases responding significantly to trastuzumab plus pertuzumab.*

CASE REPORT

1. Case report 1

We present the case of a 59-year-old man with a history of rectal adenocarcinoma in March 2017. He underwent low anterior resection, with final pathology revealing stage IIIB (T3, N2a, M0 American Joint Committee on Cancer 7th edition). He finished 5 months of adjuvant chemotherapy with mFOLFOX6 regimen and stopped due to anaphylaxis with Oxaliplatin. In July 2019, peritoneal metastasis was found in imaging. The molecular profile revealed RAS and BRAF wide-type, HER2 amplification (3+) in immunohistochemistry (IHC), and there was no mutation found by next-generation sequencing on the tumor specimen. FOLFIRI plus bevacizumab was recommended. He received 6 months of FOLFIRI plus bevacizumab, followed by irinotecan plus bevacizumab. Two years later, in September 2019, his disease progressed to the lungs. Because of positive HER2 amplification, treatment with trastuzumab combined with pertuzumab was initiated because this is the only anti-HER2 drug available in Vietnam. The patient tolerated the treatment well. A repeated CT scan after 12 weeks (about three months) of treatment showed a significant response (*Figure 2*). Treatment was continued and re-evaluation was done every three months. His disease remained responsive until August 2022, when the lung lesion progressed again (*Figure 4*). Subsequence therapy has continued until now. Dual anti-HER2 therapy improved his progression-free survival by 11 months, which was a remarkable benefit for second-line stage IV rectal cancer.

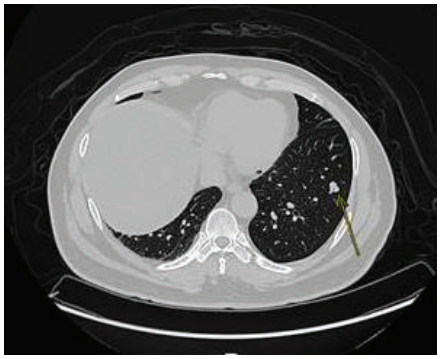

Figure 1. Lung metastasis.

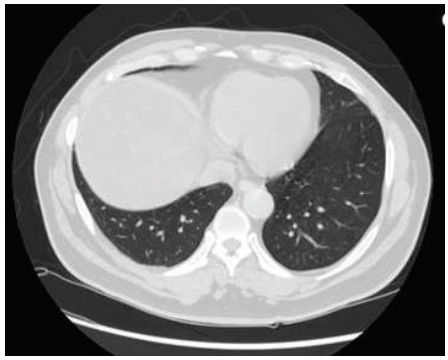

Figure 2. Lung lesion responded after 12 weeks of treatment.

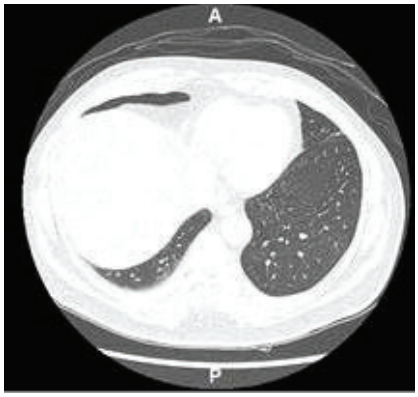

Figure 3. Response remained for 11 months.

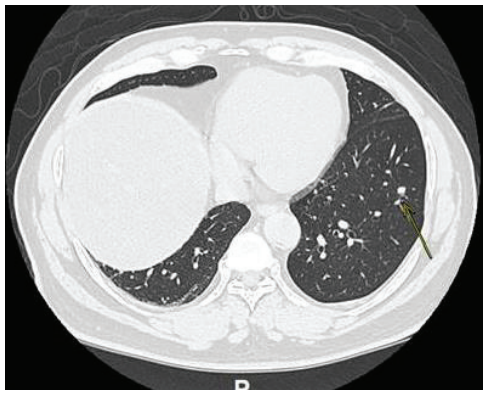

Figure 4. Lung lesion developed again.

2. Case report 2

A 65-year-old male presented in July 2023 with a bowel obstruction due to a mass in the hepatic flexure of the colon. The patient underwent an extended right hemicolectomy with lymph node dissection. Histology revealed moderately differentiated adenocarcinoma, with negative node metastasis, prominent lymphovascular, and perineural invasion. During the operation, multiple lesions in the liver were found. Finally, he was diagnosed with stage IV colon cancer. IHC revealed intact (proficient) DNA mismatch repair proteins (pMMR). The molecular profile revealed KRAS and BRAF wide-type, HER2 amplification (3+) in IHC. Bevacizumab plus mFOLFOX6 was initiated. After 6 cycles of chemotherapy, the patient achieved a partial response. However, he did not tolerate well with chemotherapy (nausea, loss of appetite, weight loss, etc.); the treatment was changed to 5-Fluorouracil (5-FU) combined with Bevacizumab. Five months later, there

was a progression of the disease as CT imaging showed growing hepatic lesions. Based on the tumor genetic profile and the fact that the patient had experienced poor tolerance to chemotherapy, dual HER2-targeted therapy with trastuzumab and pertuzumab was administered. The patient tolerated the treatment well. A repeated CT scan after 12 weeks (about three months) of treatment showed a partial response (*Figure 6*), and the CEA level decreased dramatically from 617 ng/mL to 60 ng/mL. The treatment was continued and re-evaluation was done every three months. His disease remained responsive for 7.5 months when hepatic lesions progressed again (*Figure 7*), and the CEA level increased to 1022 ng/mL. Dual anti-HER2 therapy improved his progression-free survival by 7.5 months, which was a remarkable benefit for second-line stage IV rectal cancer and especially for those who could not tolerate well with chemotherapy.

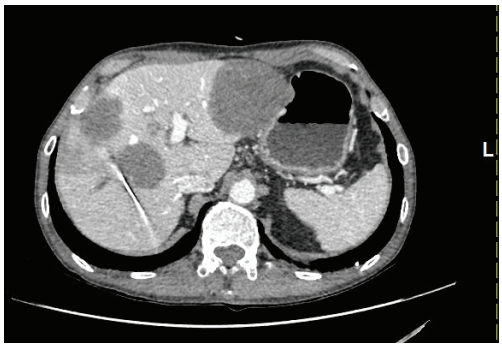

Figure 5. Multiple liver metastases.

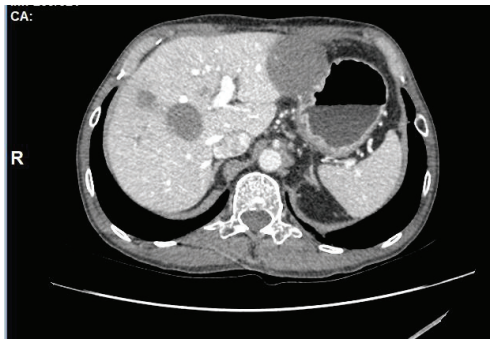

Figure 6. Partial response was achieved after 3 months.

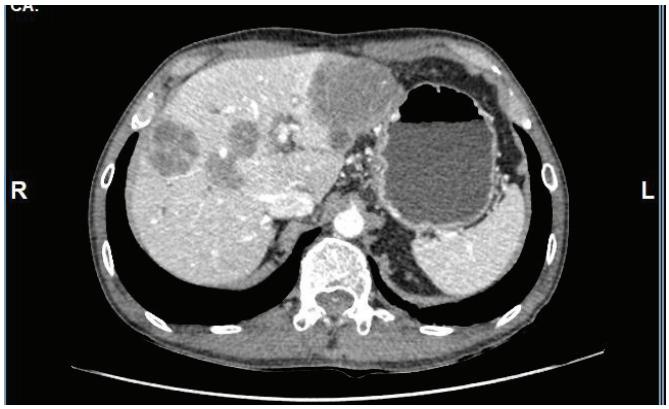

Figure 7. Progression was seen after 7.5 months.

DISCUSSION

HER2 amplification represents approximately 2% of all stage IV CRCs and is associated with resistance to EGFR-based treatment [5, 6]. HER2 overexpression is defined as ≥ 50% staining by IHC or ≥ 10% staining by IHC and positive amplification by fluorescent in situ hybridization according to HERACLES diagnostic criteria [7]. Amplification or overexpression of HER2 oncogene causes hyperactivation of mitogenic signals, even without ligand binding, thereby leading to uncontrolled cell proliferation and tumorigenesis [8].

While clinical studies on the combination of trastuzumab and pertuzumab in metastatic colon cancer are still limited, there is a growing body of evidence supporting the efficacy of HER2-targeted therapies in this context. Early-stage studies and retrospective analyses have demonstrated that a subset of mCRC patients with HER2 amplification or overexpression can benefit from treatment with HER2 inhibitors. However, the response rates in mCRC are often lower compared to breast cancer, underscoring the need for a more precise selection of patients who are likely to benefit.

The combination therapy of trastuzumab plus pertuzumab showed promising results for patients with treatment-refractory HER2-Amp mCRC in the single-arm, phase IIa MyPathway multibasket study and is listed in the National Comprehensive Cancer Network guidelines for HER2-Amp mCRC along with trastuzumab plus lapatinib or fam-trastuzumab deruxtecan-nxki as a category 2A recommendation. Trastuzumab plus pertuzumab demonstrated an objective response rate of 32% with a median OS of 11.5 months and a median progression-free survival of 2.9 months in MyPathway [9]. Similar efficacy was observed with trastuzumab plus pertuzumab in the multicenter phase II TRIUMPH study [10]. However, the clinical response is heterogeneous, and not all HER2-positive CRCs respond to these therapies. Factors such as tumor heterogeneity, mutation status, and co-expression of other biomarkers, such as HER3, EGFR, or PI3K, may influence treatment outcomes. This highlights the need for further studies to refine patient selection criteria and identify those who are most likely to benefit from dual HER2 blockade.

In our case, we present a patient diagnosed with HER2-positive metastatic colon cancer who was treated with a combination of trastuzumab and pertuzumab. The patient had previously failed standard chemotherapy regimens and was found to have HER2

overexpression, which guided the decision to pursue targeted therapy. Our patient experienced stabilization of the disease for several months, indicating that dual HER2 blockade may slow the progression of metastatic disease in HER2-positive colon cancer. This is consistent with findings from clinical trials such as the HERACLES trial, which reported disease stabilization in some patients treated with HER2-targeted agents.

While the patient showed clinical benefit, there were several challenges encountered during treatment. One significant concern was the potential for cardiotoxicity, a well-documented side effect of trastuzumab. Our patient underwent regular cardiac monitoring, and fortunately, no significant changes in left ventricular ejection fraction were observed. Nonetheless, the risk of cardiotoxicity remains a concern in HER2-targeted therapies, and careful cardiac surveillance is essential, particularly in patients with existing comorbidities. Another challenge in this case was treatment resistance. Despite the partial response and stabilization, HER2-targeted therapies often face issues with acquired resistance over time. In our patient, there was concern that the disease may eventually progress due to changes in the tumor microenvironment or the emergence of HER2-negative clones. Monitoring disease progression and considering subsequent lines of therapy, such as combination with other targeted agents or immune checkpoint inhibitors, will be crucial for the long-term management of this patient.

CONCLUSION

These cases highlight the potential benefits of trastuzumab and pertuzumab as a treatment options for patients with HER2-positive metastatic colon cancer. The patient showed a promising partial response and disease stabilization, suggesting that this combination therapy can provide clinical benefit in a subset of mCRC patients. However, the challenges of side effects, resistance, and the need for careful patient selection remain important considerations. Future research and clinical trials will be essential to validate the efficacy of dual HER2 blockade in metastatic colon cancer, refine treatment strategies, and explore the role of combination therapies to further improve patient outcomes.

Ethics: The study was conducted with transparent, honest information, data, and methods. The research results were evaluated objectively and accurately. Vinmec Times City International Hospital granted permission for the use and publication of the research data. The authors declare to have no conflicts of interest in the study.

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