JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Case Report

J Oncol Pharm Practice
1–6

DOI: 10.1177/10781552221074973
journals.sagepub.com/home/opp
SAGE

The drugs screened by OncoVee™-Mini-PDX have significantly benefited the patient with HER2-positive advanced gastric cancer

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Abstract

Introduction: At present, the prognosis of HER2-positive advanced gastric cancer is extremely poor, and some patients fail to benefit from first-line Herceptin treatment, thus facing difficulties in choosing second-line drugs.

Case Report: Here, we report a 61-year-old male patient with HER2-positive advanced gastric cancer who is primarily resistant to Herceptin and has poor therapeutic effect.

Management & Outcome: Afterwards, the OncoVee™-MiniPDX-guided anticancer method was used to screen drugs for second-line treatment, which resulted in liquefaction and necrosis of the patient's lesions and improved liver function indicators, as well as rapid relief of the patient's clinical symptoms.

Discussion: In the treatment of the Herceptin-resistant patient with advanced gastric cancer, OncoVee™-MiniPDX method screened drugs and brought clinical benefits.

Keywords

mini-PDX, advanced gastric cancer, HER2-positive

Date received: 27 September 2021; revised: 5 January 2022; accepted: 5 January 2022

Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide.[1] It is estimated that GC causes more than 7,00,000 deaths annually, representing the third leading cause of cancer deaths, mainly due to the advance stage present at the diagnosis.[2–4]

With the development of gene sequencing technology, the era of precision treatment of GC has come. Among the many molecular targets currently in clinical research, human epidermal growth factor receptor 2 (HER2) is the one with the clearest clinical significance and the most widely used. HER2 has tyrosine kinase activity and plays an important role in the occurrence and development of tumors.[5] The positive rate of HER2 in GC is about 12%-20%.[6]

Previous studies have demonstrated that HER2 signaling pathway is a key driver of carcinogenesis and tumor progression in approximately 7% to 34% of total patients with GC.[4,7,8] Targeting HER2 combined with chemotherapy has been the first-line treatment for HER2-positive advanced GC.[8,9] However, only a few patients with HER2-positive GC respond to the HER2-targeting agents.

Recently, there have been increasing interests in the development and characterization of patient-derived xenograft (PDX) tumor models for cancer research.[10] PDX models retain the principal histologic and genetic characteristics of donor tumors and remain stable throughout passages. These models have been proven to predict clinical outcomes and are used for preclinical drug evaluation,

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biomarker identification, biological research and personalized drug strategies.[11–13] Therefore, the PDX model can be used to summarize the complexity and heterogeneity of gastric cancer. However, directly applying the traditional PDX model to patients with gastric cancer has limitations. It usually takes 4 to 8 months for the established PDX model to be ready for the assessment of drug sensitivity, and the treatment time for gastric cancer patients who have begun drug sensitivity guidance is too long. The mini-PDX model (OncoVee^{TM}-MiniPDX®, LIDE Biotech, Shanghai, China) provides an effective alternative because it takes only about 7 days to complete the drug sensitivity test, which can provide guidance for each patient's rapid and personalized selection of individual drugs.

Here, we report a 61-year-old male patient with HER2-positive advanced GC who adjusted the treatment regimen according to the results of the mini-PDX model and benefited from it.

Case report

A 61-year-old male patient came to our hospital due to pain and discomfort under the xiphoid process for 6 months. During the course of the illness, the patient had a slight sense of obstruction when eating, and his symptoms gradually worsened. Gastroscopy on 27 April, 2019 showed a mass in the esophagus and cardia. The pathology revealed poorly differentiated adenocarcinoma (Figure 1A), and immunohistochemistry showed the expression of HER2 (3 +) (Figure 1B). Chest and abdomen computed tomography (CT) scan showed thickening of the wall of the gastric cardia, narrowing of the lumen, enlarged lymph nodes around it, and multiple metastatic lesions in the liver (Figure 2A). According to the 8th edition gastric cancer stage classification, his disease was clinically staged as IV ($cTxN_+M1$) and was therefore inoperable.

Due to the high burden of liver metastases and elevated liver function transaminase and bilirubin, as a first-line treatment, the combination therapy given includes oral capecitabine 1.5 g twice a day on days 1–14, and trastuzumab (Herceptin) 550 mg on day 1. Unfortunately, after two cycles, the patient's symptoms worsened, the tumor foci increased (Figure 2B), bilirubin and transaminase gradually increased (Figure 2C&2D), and the patient's condition was evaluated as PD on June 9, 2019 based on the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).

At the same time of the above treatment, mini-PDX model drug sensitivity test was conducted on the liver biopsy tumor tissue (Figure 3A), and the results indicated that the patient was sensitive to docetaxel and apatinib, but not to Herceptin, capecitabine and platinum drugs (Figure 3B). Subsequently, as a second-line treatment, considering that the patient's condition is heavier, we have reported to the hospital ethics committee and fully communicated with the patient and the family, decided to use a combination therapy, which consisting of 250 mg of apatinib once a day and 40 mg of docetaxel once a week. Fortunately, after one month of treatment, the patient's clinical symptoms improved rapidly, liver metastases gradually shrink or liquefy necrotic (Figure 4A), and transaminase and bilirubin decreased significantly (Figure 4B&4C). Although the patient benefited from guided treatment for several months, he eventually developed liver failure due to severe liver metastases, refused further treatment, and died shortly thereafter.

Discussion

Anti-HER2 therapies are beneficial for patients with HER2-positive gastric cancer, ToGA study laid the

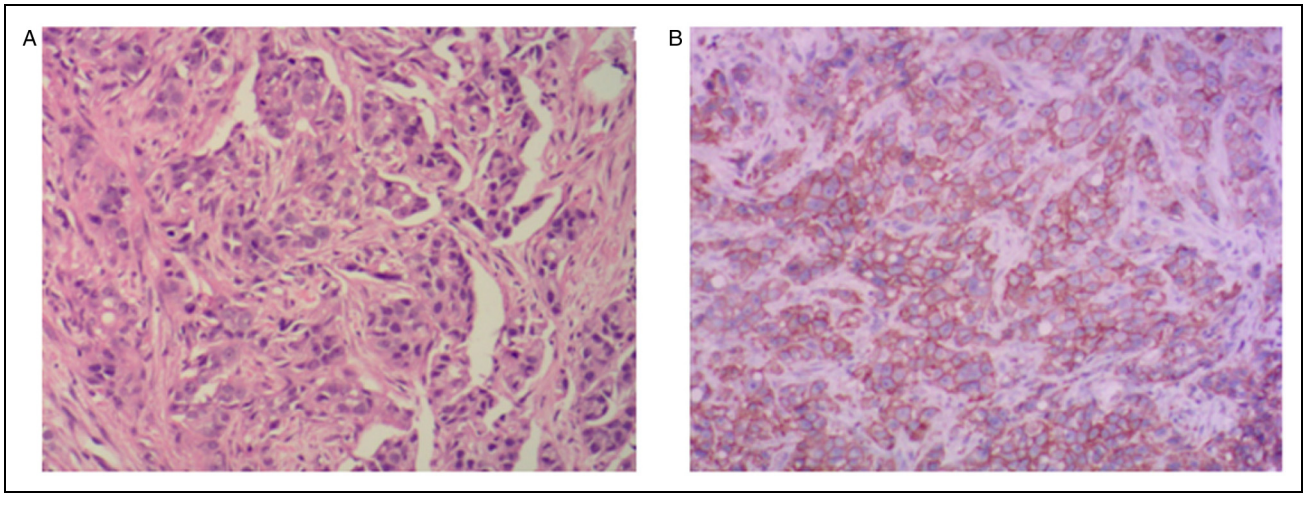

Figure 1. (A) gastroscopy pathology: hematoxylin and eosin staining indicating poorly differentiated adenocarcinoma (100×). (B) Immunohistochemistry showing the expression of HER2 (+++) (100×).

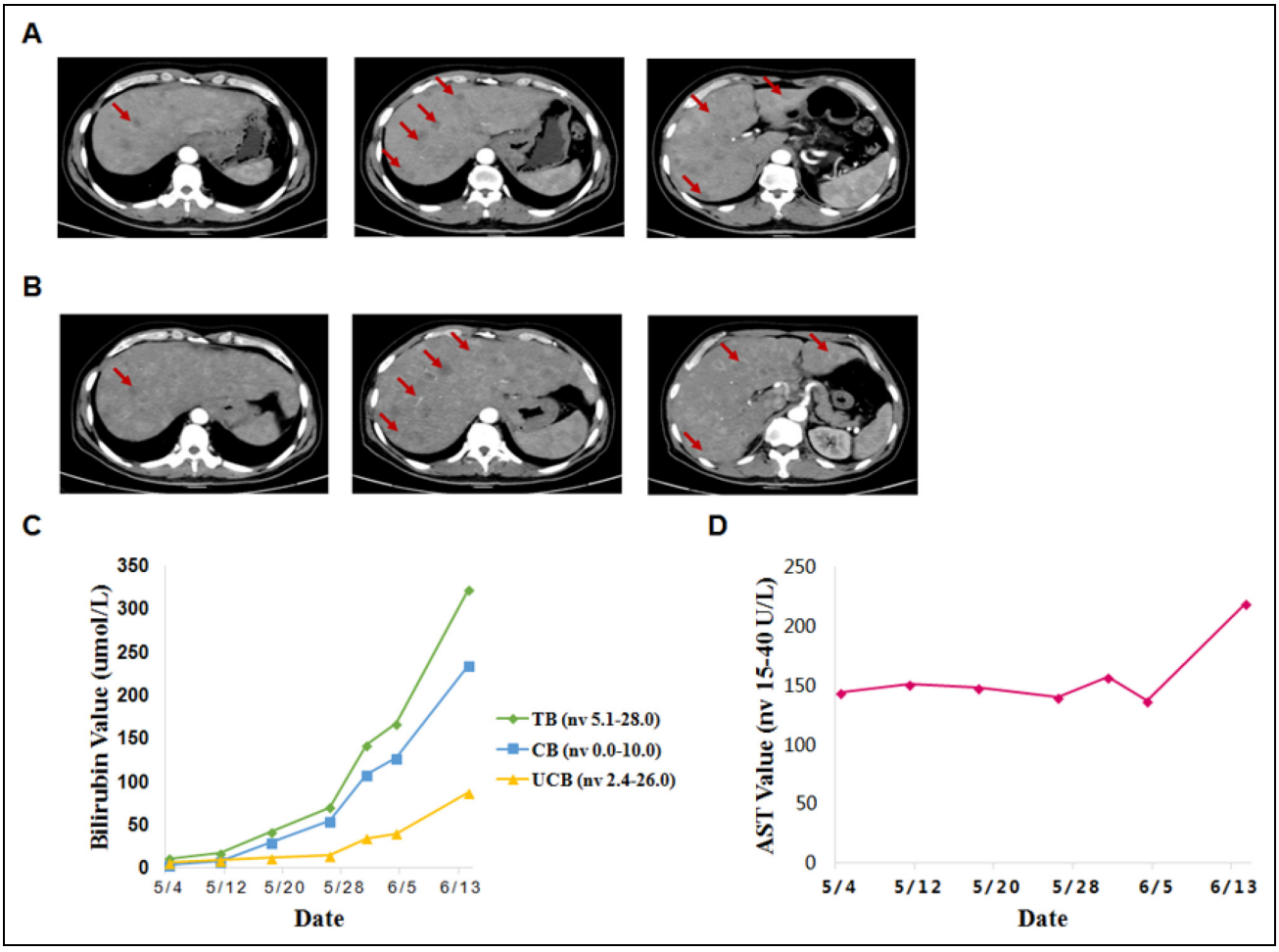

Figure 2. (A) Computed tomography at the first presentation showing multiple uneven density foci in the liver (mediastinal window). The red arrows indicated liver metastases. (B) Computed tomography showing changes in liver metastases after treatment with Herceptin (Mediastinal window). The red arrows indicated liver metastases. (C) The curve showing the changes of bilirubin, which included total bilirubin (TB), conjugated bilirubin (CB) and unconjugated bilirubin (UCB). (D) The curve showing the changes of transaminase AST.

foundation for trastuzumab in the first-line treatment of HER2-positive GC.[8] To our knowledge, although anti-HER2 therapy has a significant effect, there is still a subset of patients with gastric cancer who do not benefit and need to be given an effective second-line regimen.

Studies have shown that there are a variety of reasons leading to drug resistance in targeted therapy of HER2, including primary and required resistance. The main mechanisms of primary resistance are as follows: (1) Tumor heterogeneity. GC is a highly heterogeneous malignant tumor with a complex genomic landscape of molecular alterations. Prominently, HER2 expression is highly discrepant between primary and metastatic disease.[14,15] In the GASTHER1 study, 5.7% initial HER2-negative patients on primary tumor resulted HER2-positive on metastatic sites, reaching 17% discordance for liver lesions.[16] (2) Co-existing oncogenic alterations. Oncogenic alterations such as point mutations or amplification have been recorded, leading to the activation of downstream pathways and hampering the inhibitory effect of HER2-directed agents.[17] PI3KCAactivating mutations and/or PTEN loss may cause constitutive activation of the AKT–mTOR pathway, and the constitutive/aberrant activation of this signaling cascade leads to ineffective inhibition of HER2.[18–20] Hyperactivation of the hepatocyte growth factor (HGF) or the amplification of mesenchymal–epithelial transition (MET) may be involved in the primary resistance of GC.[21–23] Furthermore, HER2 and HER1 may co-amplify in about 7% of GCs, according to the TCGA database report.[24] Preclinical studies showed that those cases may be resistant to upfront trastuzumab, while dual inhibitors might be beneficial in obtaining a more complete growth inhibition.[25] The cases we report are largely considered to be primary drug resistance; thus, further treatment selection is an urgent issue that needs to be addressed. In this case, the screening of therapeutic

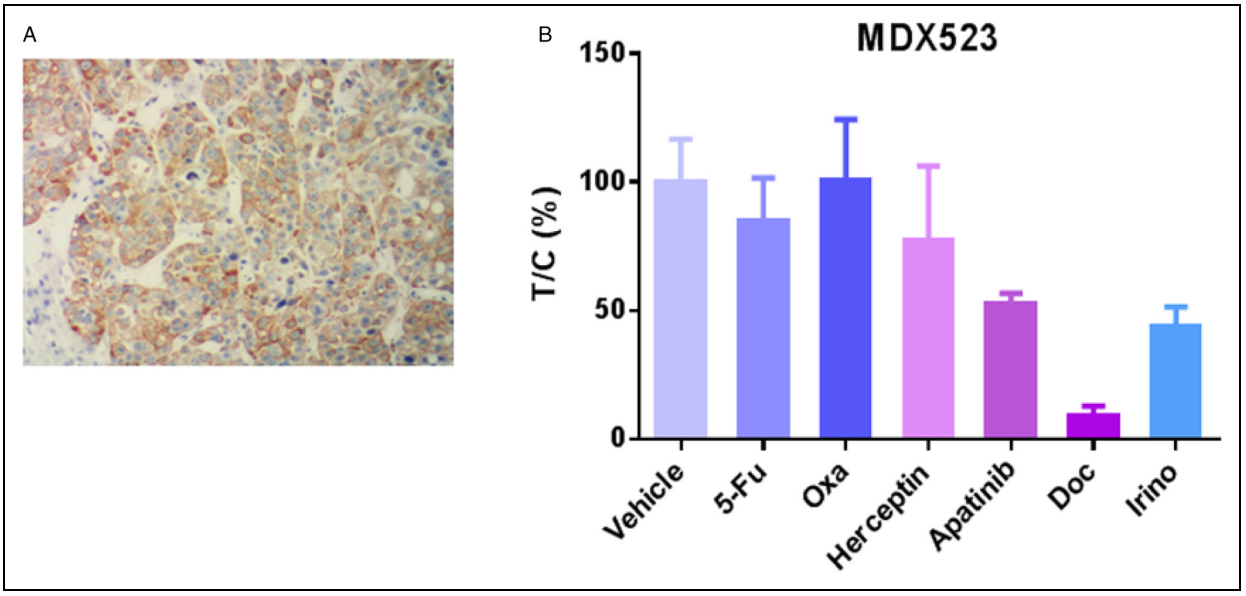

Figure 3. (A) liver puncture pathology indicated gastric cancer liver metastasis (100×). (B) The mini-PDX model was used to determine the sensitivity of the tumor to various drugs, which included fluorouracil, oxaliplatin, Herceptin, apatinib, docetaxel, and irinotecan.

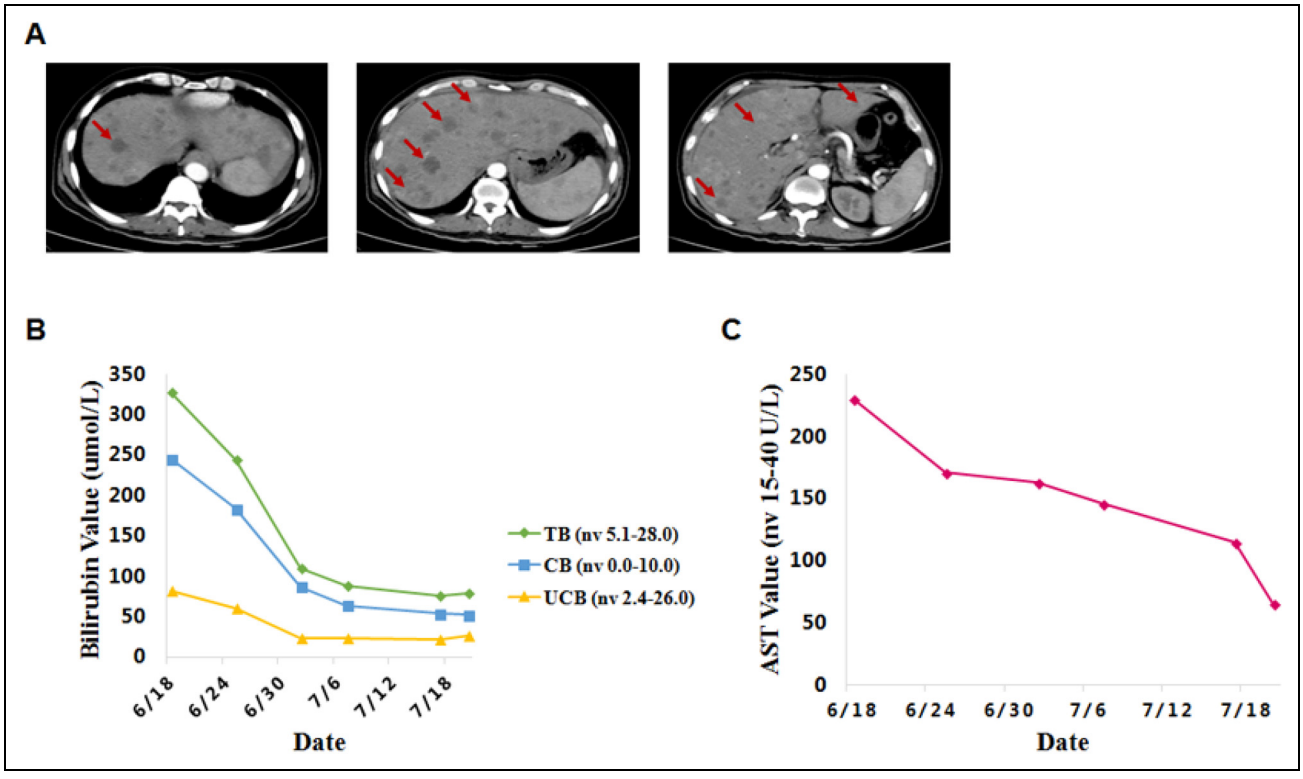

Figure 4. (A) CT shows changes in liver metastasis (mediastinal window) following minn-PDX-guided drug therapy, with focal shrinkage or liquefaction necrosis. (B) The curve showing the changes of bilirubin, which included total bilirubin (TB), conjugated bilirubin (CB) and unconjugated bilirubin (UCB). (C) The curve showing the changes of transaminase AST.

agents through the OncoVee^{TM}-MiniPDX model produced clinical benefits for this patinet with HER2-positive gastric cancer.

Most transformational cancer research requires effective preclinical models.[26] The preclinical PDX models have overcome the limitations of conventional cell line-based

models and are now more commonly used. These models can provide drug sensitivities that mimic the clinical response of cancer patients to cytotoxic agents. Similarly, since PDX models correlate well with the pathological genetic characteristics of individual patient tumors, they are becoming the preferred preclinical tool for improving the drug development process.[27] However, the long time in establishing PDX models restrains their usage in more aggressive cancers like GC. OncoVee^{TM}-MiniPDX is a platform with lower complexity and faster turnover of results. It is a promising tool in which tumor cells from patients remain tumorigenic and then inoculated into immunocompromised mice via special capsules to establish tumor xenografts. This kind of individualized treatment provides a scientific rationale for clinical therapy and avoids the side effects from clinical experience-guided medication. It is demonstrated that the mini-PDX sensitivity assay using fresh tumor samples is of high predictive power with a sensitivity of 80% and a specificity of 93%.[28] In this case, the results of OncoVee^{TM}-MiniPDX sensitivity test and apatinib + docetaxel regimen were adopted, and the patient had significant clinical benefits.

In conclusion, after Herceptin resistance in the patient with HER2-positive gastric cancer, the drugs screened by OncoVee^{TM}-MiniPDX method brought clinical benefits in this case. Further research is warranted using the OncoVee^{TM}-MiniPDX method in patients with gastric cancer.

List of abbreviations

GC: gastric cancer; HER2: human epidermal growth factor receptor 2; PDX: patient-derived xenograft; PS: performance status; CT: computed tomography; RECIST: Response Evaluation Criteria in Solid Tumors; PFS: progression-free survival; OS: overall survival.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of Nanjing First Hospital. The patients/participants provided their written informed consent to participate in this study. The animal study was reviewed and approved by the ethics committee of Nanjing First Hospital.

Consent for publication

Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Health Science and Technology Development Foundation of Nanjing (grant number JQX18004).

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