Effectiveness of Trastuzumab Combined With Capecitabine Treatment in a Patient With Hilar Cholangiocarcinoma Complicated by Liver Metastases With an ERBB2-Activating Mutation: A Case Report

Daobing Zeng1,2, Xiaofei Zhao1,2, Liang Di1,2, Luyan Lou3, Yanfang Song3, Yanrui Zhang3, Huanhuan Liu3 and Guangming Li1,2*

1 General Surgery Department, Beijing Youan Hospital, Capital Medical University, Beijing, China, 2 Clinical Center for Liver Cancer, Capital Medical University, Beijing, China, 3 Medical Affairs Department, Acommed Biotechnology Co. Ltd., Beijing, China

The identification of ERBB2 (HER2) alteration in some solid tumors has become critically important due to the actionable events predictive of response to anti-HER2 therapy. However, the efficacy of ERBB2 mutated hilar cholangiocarcinoma (hCCA) against ERBB2 is rarely reported. Here we report a 76-year-old female diagnosed with hCCA complicated by liver metastases after radical resection. The next-generation sequencing assay showed that the tumor had an ERBB2 mutation. Then, the patient was treated with trastuzumab plus capecitabine. After 2 months of treatment, she had a partial response. Until now, the patient is still alive. This study has shown the potential of trastuzumab combined with capecitabine as an effective treatment for hilar cholangiocarcinoma complicated by liver metastases harboring ERBB2 alterations.

Keywords: cholangiocarcinoma, ERBB2 mutation, treatment, trastuzumab, case report

INTRODUCTION

Cholangiocarcinoma (CCA) is a heterogeneous malignancy that can occur at every point in the biliary tree, from the canals of Hering to the main bile duct (1). CCAs are classified into intrahepatic (iCCA) and extrahepatic (eCCA) categories on the basis of anatomical origin (2). The eCCA can be further separated into two subtypes: the proximal or hilar (HCCA) accounts for 60–70% and the distal for 20–30% of CCA (3).

hCCA is a common malignant tumor with a relatively poor prognosis. The overall 5-year survival rate is approximately 13–40% (4). The gold standard of treatment for patients with...
unresectable hilar cholangiocarcinoma is palliative chemotherapy. However, there was a poor outcome with radiation and systemic chemotherapy, such as with gemcitabine and cisplatin (5). Thus, a novel therapeutic approach is warranted.

Targeted therapies are rapidly transforming the therapeutic paradigm for biliary tract cancer, particularly for iCCA, where targeting FGFR2 fusions, IDH 1/2 mutations, and BRAF V600E mutations are becoming a reality (6, 7). Unlike iCCA, targeted therapies for hCCA are rare.

Herein we report a rare case of a female patient with ERBB2-mutant hCCA who responds well to the treatment of trastuzumab in combination with capecitabine.

CASE PRESENTATION

A 76-year-old woman was admitted to a local hospital after she experienced itchy skin plus dark yellow urine for several days. The patient was diagnosed with Bismuth type IV hCCA after imageological diagnosis and received percutaneous transhepatic cholangiodrainage (PTCD) on February 5, 2021. The total bilirubin concentration was 400 µmol/L before PTCD, and the daily bile drainage was approximately 300-400 ml. The preoperative total bilirubin level was reduced to the normal level of 19.6 µmol/L. Then, she visited Beijing Youan Hospital, Capital Medical University, for further operative treatment. Enhanced CT of the upper abdomen and magnetic resonance cholangiopancreatography revealed a low-density mass in the left medial hepatic lobe of the liver. After receiving multidisciplinary treatment, the patient had a partial response (PR). We then continued to treat the patient with trastuzumab combined with capecitabine. After another 2 months, the lesion diameter was still 13 mm, which was considered a stable disease (SD), and no metastatic lesions in other organs were found. In addition, the levels of serum tumor markers were significantly reduced during the treatment (Figure 1). At the time of this report, the patient was alive.

DISCUSSION

Advances in genomic research have promoted the development of personalized medicine for the treatment of cancer patients. Here we reported an hCCA patient harboring the ERBB2 R678Q mutation who acquired a response to trastuzumab and capecitabine treatment. To our knowledge, this is the first report to claim that ERBB2 mutations can be used as trastuzumab targets in hCCA.

ERBB2-targeted therapy has achieved remarkable success in the treatment of metastatic breast cancer and gastric cancer. Similarly, recent studies have identified that patients with ERBB2 overexpression or amplification could potentially benefit from ERBB2-targeted therapy in biliary tract cancer (trastuzumab, not lapatinib, has therapeutic effects on Chinese patients with HER2-positive cholangiocarcinoma) (8)[Law, 2012 #21;Law, 2012 #21]. Jeong reported that a biliary tract cancer patient with HER2 overexpression received trastuzumab-pkrb, gemcitabine, and cisplatin and showed an overall response rate of 50.0% (including SD and PR) (9). Yarlagadda et al. demonstrated that

| Gene | Exon | Mutation | Variation frequency |
|------|------|----------|---------------------|
| ERBB2 | Exon 17 | R678Q | 41.60% |
| PTCH1 | Exon 6 | c.747-2A>T | 32.25% |
| TP53 | Exon 8 | E286Q | 27.05% |
| ARID1A | Exon 20 | Q2176X | 25.78% |
| SMAD4 | Exon 12 | D493Y | 26.71% |
| SMAD4 | Exon 9 | R861H | 3.98% |

TABLE 1 | Summary of gene test results and mutations that may have clinical significance.
a CCA patient with ERBB2 amplification was treated with dual HER2-directed therapy (trastuzumab/pertuzumab) and responded very well with regression of tumor on imaging (10). Consistent with this result, our study showed that an hCCA patient with ERBB2 mutated can benefit from capecitabine combined with trastuzumab treatment. This may implicate that ERBB2-targeted therapy could be a favorable option in hCCA with ERBB2 variation.

ERBB receptors contain an extracellular domain (ECD), a transmembrane domain (TMD), an intracellular region that consists of a juxtamembrane domain (JMD), a kinase domain, and a carboxy terminal tail domain (11). Several studies reported that TMD variation and ECD of ERBB2 may stabilize ERBB2 heterodimerization with other EGFR family members and favor a kinase-active conformation (12). TMD variations are located within the glycine zipper motif at the N-terminal portion of TMD, which is critically important to the dimerization of ERBB2 to other EGFR family members (12).

Trastuzumab is a monoclonal antibody specifically designed to target the ERBB2. The mechanisms of action of trastuzumab include antibody-dependent cellular cytotoxicity, antibody-mediated ERBB2 internalization followed by receptor degradation, and inhibition of ERBB2 dimerization (13). ERBB2 amplification with corresponding HER2 protein overexpression is associated with sensitivity to therapies targeting HER2, including lapatinib, pertuzumab, and trastuzumab, which were approved by the US Food and Drug Administration. Recent evidence has demonstrated that the presence of ERBB2 mutation can predict clinical responses to anti-HER2-targeted therapies (14).

The recent results from the SUMMIT study have shown that the clinical benefit from ERBB2-targeted therapies (neratinib) may be dependent on the type of ERBB2 alteration and type of tumor (15). Mou et al. reported that a CCA patient with ERBB2 gene S310F in the ECD received trastuzumab combined with chemotherapy and showed therapeutic effects, decreased tumor burden, and improved quality of life (16). Herein we found an hCCA patient, with Pahuja et al. indicating that the ERBB2 R678Q mutation located at the JMD might have a significant effect on TMD geometry and dimerization (17). Therefore, we speculated that the JMD mutant R678Q might respond to trastuzumab.

**CONCLUDING REMARKS**

In conclusion, we were able to identify ERBB2 JMD mutations on NGS in a patient with hCCA and found anti-HER2 therapy as an effective treatment strategy. This will have implications for other patients with hCCA in terms of the identification of this target and considerations toward anti-HER2 therapy on or off trial.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article.supplementary materials. Further inquiries can be directed to the corresponding author.

**ETHICS STATEMENT**

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

**AUTHOR CONTRIBUTIONS**

XZ and LD participated in collecting data. LL and YS drafted the manuscript. HL and YZ revised and commented on the draft. DZ and GL contributed to the scientific review and final approval of this manuscript. All authors read and approved the final manuscript.
REFERENCES

1. Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, et al. Expert Consensus Document: Cholangiocarcinoma: Current Knowledge and Future Perspectives Consensus Statement From the European Network for the Study of Cholangiocarcinoma (ENS-GCCA). Nutr Rev Gastroenterol Hepatol (2016) 13(5):261–80. doi: 10.1038/nrgastro.2016.51

2. Bertuccio P, Malvezzi M, Carioli G, Hashim D, Boffetta P, El-Serag HB, et al. Global Trends in Mortality From Intrahepatic and Extrahepatic Cholangiocarcinoma. J Hepatol (2019) 71(1):104–14. doi: 10.1016/j.jhep.2019.03.013

3. Sapisochin G, Iainc T, Subramanian V, Doyle M, Heimbach JK, Hong JC. Multidisciplinary Treatment for Hilar and Intrahepatic Cholangiocarcinoma: A Review of the General Principles. Int J Surg (2020) 82c:77–81. doi: 10.1016/j.ijsu.2020.04.067

4. Ma Y, Chen Z, Zhu W, Yu J, Ji H, Tang X. Chemotherapy Plus Concurrent Irreversible Electroporation Improved Local Tumor Control in Unresectable Hilar Cholangiocarcinoma Compared With Chemotherapy Alone. Int J hyperthermia: Off J Eur Soc Hyperthermic Oncol North Am Hyperthermia Group (2021) 38(1):1512–8. doi: 10.1080/02656736.2021.1991008

5. Yamashita-Kashima Y, Yoshimura Y, Fujimura T, Shu S, Yanagisawa M, Yorozu K, et al. Molecular Targeting of HER2-Overexpressing Biliary Tract Cancer Cells With Trastuzumab Emtansine, an Antibody-Cytotoxic Drug Conjugate. Cancer chemother Pharmacol (2019) 83(4):659–71. doi: 10.1007/s00280-019-03768-8

6. Lamara R, Barrios J, McNamara MG, Valle JW. Molecular Targeted Therapies: Ready for “Prime Time” in Biliary Tract Cancer. J Hepatol (2020) 73(1):170–85. doi: 10.1016/j.jhep.2020.03.007

7. Subbiah V, Lassen U, Élèz E, Italiano A, Curigliano G, Javle M, et al. Dabrafenib Plus Trametinib in Patients With BRAF(V600E)-Mutated Biliary Tract Cancer (ROAR): A Phase 2, Open-Label, Single-Arm, Multicentre Basket Trial. Lancet Oncol (2020) 21(9):1234–43. doi: 10.1016/S1470-2045(20)30321-1

8. Law LY. Dramatic Response to Trastuzumab and Pertuzumab in a Patient With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Cholangiocarcinoma. J Clin Oncol (2012) 30(27):e271–3. doi: 12.1020/JCO.2012.42.3061

9. Jeong H, Jeong JH, Kim KP, Lee SS, Oh DW, Park DH, et al. Feasibility of HER2-Targeted Therapy in Advanced Biliary Tract Cancer: A Prospective Pilot Study of Trastuzumab Biosimilar in Combination With Gemcitabine Plus Cisplatin. Cancers (Basel) (2021) 13(2):161. doi: 10.3390/cancers13020161

10. Yarlagadda B, Kamatham V, Ritter A, Shahjehan F, Kasi PM. Trastuzumab and Pertuzumab in Circulating Tumor DNA ERBB2-Amplified HER2-Positive Refractory Cholangiocarcinoma. NPJ Precis Oncol (2019) 3:19. doi: 10.1038/s41698-019-0091-4

11. Kovacs E, Zorn JA, Huang J, Barros T, Kuriyan J. A Structural Perspective on the Regulation of the Epidermal Growth Factor Receptor. Annu Rev Biochem (2015) 84:739–744. doi: 10.1146/annurev-biochem-060614-034402

12. Fan Y, Qiu J, Yu R, Cao R, Chen X, Ou Q, et al. Clinical and Molecular Characteristics of Chinese non-Small Cell Lung Cancer Patients With ERBB2 Transmembrane Domain Mutations. Mol Oncol (2020) 14(8):1731–9. doi: 10.1002/1878-0261.12733

13. Zhao J, Mohan N, Nussinov R, Ma B, Wu WJ. Trastuzumab Blocks the Receiver Function of HER2 Leading to the Population Shifts of HER2-Containing Homodimers and Heterodimers. Antibodies (Basel) (2021) 10 (1):7. doi: 10.3390/antib10010007

14. Ross JS, Gay LM, Wang K, Ali SM, Chumsri S, Elvin JA, et al. Nonamplification ERBB2 Genomic Alterations in 5605 Cases of Recurrent and Metastatic Breast Cancer: An Emerging Opportunity for Anti-HER2 Targeted Therapies. Cancer (2016) 122(17):3654–62. doi: 10.1002/cncr.30102

15. Ross JS, Gay LM, Wang K, Ali SM, Chumsri S, Elvin JA, et al. HER Kinase Inhibition in Patients With HER2- and HER3-Mutant Cancers. Nature (2018) 554(7691):189–94. doi: 10.1038/nature25475

16. Mou HB, Li WD, Shen YJ, Shi JP, Guo XD, Yao M, et al. Trastuzumab, Not Lapatinib, Has Therapeutic Effects on Chinese Patients With HER2-Positive Cholangiocarcinoma. Hepatobiliary Pancreat Dis Int (2018) 17(5):477–9. doi: 10.1016/j.hjpdi.2018.09.011

17. Pahuja KB, Nguyen TT, Jaiswal BS, Prabhash K, Thaker TM, Senger K, et al. Actionable Activating Oncogenic ERBB2/HER2 Transmembrane and Juxtamembrane Domain Mutations. Cancer Cell (2018) 34(5):792–806.e5. doi: 10.1016/j.ccell.2018.09.010

Conflict of Interest: Author LL, YS, YZ, and HL were employed by the company Acornmed Biotechnology Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zeng, Zhao, Di, Lou, Song, Zhang, Liu and Li. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.