Advanced hepatocellular carcinoma with MET-amplified contained excellent response to Crizotinib: a case report.

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Case Report

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Abstract

**Background:** Hepatocellular carcinoma (HCC) is one of the most lethal tumors all over the world. It’s considered with extensive heterogeneity and lacks therapeutic decision-making biomarkers. There are many novel therapeutic strategies tried to prolong the survival of advanced HCC. Next-generation sequencing (NGS) is generally used for helping treatment decision which help patient benefit from genome-directed targeted.

**Case presentation:** A 56 years-old male with more than 20 years of type-B hepatitis was admitted to our department who underwent laparoscopic hepatic left lateral lobectomy because hepatocellular carcinoma. Unfortunately, tumor recurrence 1 year later. Though multiple treatments were taken, including interventional therapy, tyrosine kinase inhibitor, radiotherapy and immunotherapy, the tumor invaded his 5th thoracic vertebras and leaded to hypoesthesia and hypokinesia below the nipple line plane 2 years later. NGS was used to find potential therapeutic biomarkers. As the met amplification was identified, Crizotinib, the inhibitor of the C-Met was recommended. Tumor reduction and decreased tumor marker were observed immediately in 1 month later. And the patient has remained on remission since then.

**Conclusions:** We reported a patient with high MET amplification benefited from MET inhibitors which recommended by NGS. It indicated the potential clinical decision support value of NGS and the satisfactory treatment effect of C-met inhibitor.

**Background**

Hepatocellular carcinoma (HCC) is a kind of aggressive malignant tumor which threatened more than 600,000 people’s life in the worldwide[1]. Because of the high incidence of hepatitis virus infection, China was considered as a “Large country of liver cancer”[2]. With advancing methods, like new targeting concepts and immune therapies, clinicians not only significantly prolong the survival of patients, but also improved the quality of life. However, the response rates of these treatments were not satisfactory. The classic targeting concepts Sorafenib, for example, which was recommand as a first-line treatment therapy by almost all guidelines, was reported benefiting only about 40% of patients with HCC because of the genetic heterogeneity and other reasons[3]. The checkpoint inhibition immunotherapy, nivolumab, was reported a six-month survival rate of 83% and a nine-month survival rate of 74% with a 15% overall objective response rate (ORR)[4]. Novel therapies that combine immune checkpoint inhibitors with anti-angiogenic agents or tyrosine kinase inhibitor did demonstrate excited outcomes in advanced. Atezolizumab plus Bevacizumab reached 67.2% overall survival at 12 months and 6.8 months median progression-free survival, which much better than tyrosine kinase inhibitor alone[5]. But it’s disappointing that Lenvatinib plus pembrolizumab for the treatment of advanced HCC (NCT03713593) is established no better than Lenvatinib alone. Though these therapy had proved persistent process, the primary hepatic cancer still the top lethal tumor all over the world with a 5-year survival of 18%[3].
Due to the genomic instability of carcinoma, it presents genetic and phenotypic variation within and between tumors[6]. Correspondently, patient has not only different tumor performance but also different reaction to treatment. The side effects of treatment, such as diarrhea, hypertension and bleeding etc., also limited the efficacy of medicine. For instance, the incidence of hypertension, diarrhea, decreased appetite, and decreased weight for Lenvatinib were 42%, 39%, 34% and 31%. And about 75% of patients suffered grade 3 or higher treatment-emergent adverse events, leading to drug interruption (32.2%), dose reduction (38.1%), and drug withdrawal (7.2%)[7]. Thus, cause of response and tolerance rate, there still a part of the patients could not get either appropriate treatment or prolonged survival.

Hereby, we present a case of HCC that got satisfied partial response with Crizotinib. The fundamental information, process of diagnosis and treatment, genetic test report and evaluation of treatment effectiveness of the patient was established in this article. We expected to provide new ideas for the diagnosis and treatment of advanced HCC.

**Case Presentation**

A 56 years-old male was admitted to our department for liver mass. Because of type B hepatitis for more than 20 years, inappropriate and discontinuous anti-virus therapy, he was diagnosis slight liver cirrhosis several years before admission. There was little positive founding in his physical examination. He was diagnosis hepatocellular carcinoma with hepatitis history, elevated serum alpha-fetoprotein (51 ng/ml) and typical imaging findings. He underwent laparoscopic hepatic left lateral lobectomy on May 23, 2019. Postoperative pathology confirmed moderately to highly differentiated hepatocellular carcinoma (Fig. 1). Liver radiofrequency ablation was performed on October 19, 2020, for local tumor recurrence. However, unexpectedly, in next 2 month, another two lesions were found constantly. Thus, Lenvatinib plus Camrelizumab was applied, which was aborted 2 month later because of severe drug-induced liver injury. The patient spent more than 2 months to recover his liver function, when he was found lumbar metastases. Lenvatinib plus Camrelizumab was retaken 1 month after liver function returned to normal. Transcatheter arterial chemoembolization (TACE) was used on April 23, 2021 to inhibit the progress of tumor in liver. And stereotactic radiotherapy was taken to relief the bone destruction in May. However, tumor kept growing. Lenvatinib was replaced by Sorafenib on August 09, 2021. And he underwent TACE constantly on November 09, 2021 and December 06, 2021.

The therapy was replaced with Regorafenib plus Sintilimab after 5th thoracic vertebras metastasis in November. However, in December 2021, the patient suffered hypoesthesia and hypokinesia below the nipple line plane as 5th thoracic vertebrae metastasis progressed with spinal cord compression (Fig. 2). Thoracic vertebral lesions resection combined with thoracic laminectomy and decompression were took to release compression. The pathology of metastasis also exhibited in Fig. 1, which was a little bit different from the primary lesion's. The disease duration summary was showed in Fig. 3.

Since the common therapies for unresectable HCC, including tyrosine kinase inhibitor, checkpoint inhibition immunotherapy, radiotherapy and interventional treatment had become invalid gradually. The
patient suffered the 5th thoracic vertebra metastasis, ending to paralyze from the waist down. Though lumbar decompression was taken to help regain the exercise ability immediately, the tumor showed a rapid progression.

The next-generation sequencing was chosen to help find potential molecular targeted agents. NGS covers all the coding exons, selected introns and promoter, and analyses all gene mutations, including single-base mutation, DNA intercalation or deletion, gene copy number amplification or loss, gene fusion or rearrangement, etc. The NGS results of this patient was showed in Table 1, which showed MET amplification with copy number variations of 30.2.
Table 1
The NGS result of the patient

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Significance</th>
<th>Alteration Type</th>
<th>Coding DNA Change</th>
<th>vaf</th>
<th>CNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARAP3</td>
<td>Confirmed Somatic</td>
<td>Substitution</td>
<td>c.2716G &gt; T</td>
<td>0.194</td>
<td>-</td>
</tr>
<tr>
<td>BCORL1</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.2669G &gt; A</td>
<td>0.974</td>
<td>-</td>
</tr>
<tr>
<td>CFTR</td>
<td>Potential Significance</td>
<td>Gene Amplification</td>
<td>Amplification</td>
<td>-</td>
<td>30.2</td>
</tr>
<tr>
<td>DIS3</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.1978A &gt; G</td>
<td>0.412</td>
<td>-</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>VUS</td>
<td>Splice site</td>
<td>c.1015-3C &gt; T</td>
<td>0.480</td>
<td>-</td>
</tr>
<tr>
<td>FAT1</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.1519C &gt; T</td>
<td>0.460</td>
<td>-</td>
</tr>
<tr>
<td>MDM4</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.512-4A &gt; G</td>
<td>0.441</td>
<td>-</td>
</tr>
<tr>
<td>MET</td>
<td>Strong Significance</td>
<td>Gene Amplification</td>
<td>Amplification</td>
<td>-</td>
<td>30.2</td>
</tr>
<tr>
<td>MET</td>
<td>VUS</td>
<td>Rearrangement</td>
<td></td>
<td>0.0930578</td>
<td>-</td>
</tr>
<tr>
<td>MLH1</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.1039-8_1039-7insTTA</td>
<td>0.055</td>
<td>-</td>
</tr>
<tr>
<td>MYH11</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.3848C &gt; T</td>
<td>0.103</td>
<td>-</td>
</tr>
<tr>
<td>NPAT</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.2692A &gt; T</td>
<td>0.475</td>
<td>-</td>
</tr>
<tr>
<td>POLB</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.1002C &gt; A</td>
<td>0.618</td>
<td>-</td>
</tr>
<tr>
<td>RELB</td>
<td>Confirmed Somatic</td>
<td>Substitution</td>
<td>c.218C &gt; G</td>
<td>0.496</td>
<td>-</td>
</tr>
<tr>
<td>SERPINB4</td>
<td>VUS</td>
<td>Truncation</td>
<td>c.837T &gt; A</td>
<td>0.489</td>
<td>-</td>
</tr>
<tr>
<td>SPTA1</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.3188 + 5G &gt; A</td>
<td>0.517</td>
<td>-</td>
</tr>
<tr>
<td>SRGAP1</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.1658T &gt; C</td>
<td>0.493</td>
<td>-</td>
</tr>
<tr>
<td>SYNE1</td>
<td>Confirmed Somatic</td>
<td>Substitution</td>
<td>c.12362_12363delinsGT</td>
<td>0.566</td>
<td>-</td>
</tr>
<tr>
<td>TET3</td>
<td>VUS</td>
<td>Substitution</td>
<td>c.1207G &gt; T</td>
<td>0.478</td>
<td>-</td>
</tr>
<tr>
<td>TP53</td>
<td>Strong Significance</td>
<td>Substitution</td>
<td>c.1009C &gt; T</td>
<td>0.230</td>
<td>-</td>
</tr>
<tr>
<td>TRIO</td>
<td>VUS</td>
<td>Short indel</td>
<td>c.31_36dup</td>
<td>0.290</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: VUS: Variant of Uncertain Significance; vaf: Variant Allele Frequency; CNs: copy number variations
The patient took Crizotinib (200mg per day) since January 24, 2022. The baseline condition and images of this patient are showed in Table 2 and Fig. 4. The patient present mild anemia and acceptable liver damage. The AFP was beyond the detection range and PIVKA-II was about 75000 mAU/ml. Enhanced CT scan of abdominal showed multiple massages in liver, hilar, retroperitoneal, sacrum and ilium; right branch of portal vein invasion. The recent follow-up visit was January 31, 2023, and the condition and images (taken at December 16, 2022) was showed in Table 2 and Fig. 5. The patient gained excellent tumor remission through the target treatment. The tumor markers including AFP and PIVKA-II declined to normal range (Fig. 6) while the routine blood and hepatorenal function tests were stable. The advanced CT scan showed that the diameter of tumor was reduced observably and even disappeared at several sites.

### Table 2
**The basic line and recent stage of the patient**

<table>
<thead>
<tr>
<th>Items</th>
<th>Result</th>
<th>Reference Interval</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basic line</td>
<td>Recent</td>
<td></td>
</tr>
<tr>
<td>Wbc</td>
<td>4.8</td>
<td>3.5</td>
<td>3.5 ~ 9.5</td>
</tr>
<tr>
<td>Hb</td>
<td>110</td>
<td>127</td>
<td>130 ~ 175</td>
</tr>
<tr>
<td>Plt</td>
<td>110</td>
<td>110</td>
<td>125 ~ 350</td>
</tr>
<tr>
<td>PT</td>
<td>12.6</td>
<td>23</td>
<td>9.4 ~ 12.5</td>
</tr>
<tr>
<td>INR</td>
<td>1.08</td>
<td>2.01</td>
<td>0.82 ~ 1.15</td>
</tr>
<tr>
<td>Alb</td>
<td>34.5</td>
<td>34.1</td>
<td>40.0 ~ 55.0</td>
</tr>
<tr>
<td>ALT</td>
<td>40</td>
<td>25</td>
<td>9 ~ 50</td>
</tr>
<tr>
<td>AST</td>
<td>92</td>
<td>27</td>
<td>15 ~ 40</td>
</tr>
<tr>
<td>T-bil</td>
<td>15</td>
<td>12</td>
<td>0 ~ 21</td>
</tr>
<tr>
<td>D-bil</td>
<td>7</td>
<td>6</td>
<td>0 ~ 5</td>
</tr>
<tr>
<td>γ-GT</td>
<td>70</td>
<td>15</td>
<td>10 ~ 60</td>
</tr>
<tr>
<td>Cr</td>
<td>36</td>
<td>53</td>
<td>57 ~ 97</td>
</tr>
</tbody>
</table>

**Abbreviations:** Wbc: white blood cell count; Hb: hemoglobin; Plt: platelet; PT: prothrombin time; INR: international normalized ratio; Alb: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-bil: total bilirubin; D-bil: direct bilirubin; γ-GT: γ-glutamyl transpeptidase; Cr: creatinine.
Discussion And Conclusions

MET is a proto-oncogene encoding a receptor tyrosine kinase c-MET for hepatocyte growth factor (HGF) [8], which has been proved playing an important role in tumor onset and progression in different tumor types[9, 10]. Once MET was highly activated, it contributed to biogenesis in an autophagy-independent manner through the pathways including the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), v-srcavian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (SRC), and signal transducer and activator of transcription (STAT), leading to the progress of cancer[11, 12]. The MET pathway altered in several ways including MET overexpression, MET amplification, MET mutations[13]. Though MET overexpression had been found in about 27.9% of patients, it’s less associated with tumor recurrence or survival of patients and MET gene amplification[14, 15]. MET amplification has been found in various types of tumors, although rare, including non-small cell lung cancer (NSCLC) (1–5%)[16, 17], gastric (6.6%)[18], colorectal (4.4%)[19], and hepatocellular carcinoma (1.7%)[15].

MET amplifications had been found combined with significantly decreased STING levels and antitumor T-cell infiltration. It results in weakened IFN response mediated by STING and less tumor-infiltrating CD8 T and NK cells, leading to resistance to immune checkpoint blockade therapy[20]. Further, it used to be an acquired secondary driver in the context of EGFR or other tyrosine kinase inhibitor therapy, which leading to resistant[21–23]. Recent study proved that c-Met-mediated PARP1 phosphorylation in nucleus reducing anti-tumor effects of PARP inhibitors[24].

The HGF induced by MET was initially identified as a growth factor for hepatocytes and fibroblast-derived cell motility[25]. As previous research described, expression of c-Met is the independent prognostic factors affecting metastasis and recurrence in patients with small HCC[26]. It has been reported that the MET axis helps glucose uptake and suppresses output when also decrease hepatic glucose production by activated AMPK-dependent pathway, preventing obesity and insulin resistance [27, 28]. Triggered MET pathway would upregulate crosstalk of hepatocellular carcinoma and hepatic stellate cell to aggravate cancer[29].

Fluorescence in situ hybridization (FISH) and NGS are used to evaluated MET amplification. Either absolute gene copy number (GCN) or a ratio of MET to CEP 7 (chromosome 7 probe) ratio was reported through FISH, while NGS compare sample to either a paired normal sample or a standardized set across many genes in a particular NGS assay[13, 30]. Though FISH requires less tumor tissue than NGS, it challenged with significant inter-observer variability and variable results due to tumor sample heterogeneity. And the improvement of chromogenic in situ-hybridization would help elevated the accuracy of FISH. NGS limited by the quality of the normal sample of the non-tumoral DNA from the non-neoplastic cells in the sample. Thus, it’s generally considered that the positive results of NGS is receivable when should be doubt for the negative[10, 31, 32].

MET has been a therapeutic target in the treatment of several cancers[33]. Selective inhibitor of the MET receptor, Capmatinib, showed substantial antitumor activity in patients with advanced non-small-cell lung
cancer, especially in MET-amplified advanced NSCLC[34]. The small molecular inhibitor of c-Met, Tivantinib, had passed a randomized, double-blind, placebo-controlled, phase 3 study in MET-high hepatocellular carcinoma, which came out with 2.8 month for median progression-free survival and 10.3 months median overall survival[35].

In conclusion, we reported a rare case of advanced HCC treated with MET inhibitor, whom got excellent tumor remission. Its manifestations confirmed the potential clinical decision support value of NGS and validity of molecular targeting treatment.

**Abbreviations**

HCC  
Hepatocellular carcinoma
NGS  
Next-generation sequencing
ORR  
overall objective response rate
TACE  
transcatheter arterial chemoembolization
HGF  
hepatocyte growth factor
MAPK  
mitogen-activated protein kinase
PI3K  
phosphatidylinositol 3-kinase
Schmidt-Ruppin A-2
v-srcavian sarcoma, SRC:viral oncogene homolog
STAT  
signal transducer and activator of transcription
FISH  
Fluorescence in situ hybridization
GCN  
gene copy number
NSCLC  
non-small cell lung cancer.

**Declarations**

**Ethics approval and consent to participate**

Not applicable
Consent for publication

Informed consent was obtained by the patient for this case report presentation

Availability of data and materials

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

Competing interests

We declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Funding

Not applicable

Authors' contributions

Gu, YJ contributed to the study concept and design, collected and analyzed the data, and participated in drafting the manuscript; Xiao, M contributed to data acquisition and assisted in drafting the manuscript; Chen, ZT contributed to data acquisition and critically revised the article; Li, QY conceived the study, participated in study design and coordination, and revised the manuscript critically; all authors read and approved the final manuscript.

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Not applicable

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References


Figures

**Figure 1**

a. The primary biopsy showed moderately to highly differentiated hepatocellular carcinoma. b. The biopsy of 5th thoracic vertebras metastasis, which showed several immunohistochemical difference between

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Hepatocyte(+), AFP (partly +), Glypican-3(-), PD-1(1%), CD34(vessels +), CK19(-), Ki-67(30%), CK7(partly +), P53(-), CK8(+), CK8/18(+), HBCAg(-), HBSAg(+), HNF1B(partly +), CD10(capillary bile ducts +)

Hepatocyte(-), AFP(+), Glypican-3(+), PD-1(1%), CD34(vessels +), CK19(partly +), Ki67(60%), CK7(-), P53(70%), GS(+), Arginase-1(-), HSP70(+),
before and after.

**Figure 2**

a. The axial, coronal, sagittal plane orientation and 3D reconstruction of thoracic vertebra. The cancer invaded thoracic vertebra 5th, right adnexa and surrounding area (including intraspinal canal), leading to 4-5th thoracic vertebra spinal canal stenosis and spinal cord obviously compressed to the left.
Figure 3

The disease duration of the patient

Figure 4

a. intrahepatic multiple lesions (arterial phase); b. tumor invaded the right branch of the portal vein (portal vein phase); c. the hyperintense signal lesion after TACE (arterial phase); d. metastatic tumor in the right lung (arterial phase); f. retroperitoneal metastasis which invaded left renal vein (venous phase); g. metastases of the sacrum (arterial phase); h. metastases of ilium (arterial phase)
**Figure 5**

The lesions of liver (a. arterial phase), right lung (d. arterial phase), retroperitoneal metastasis (f. venous phase), sacrum (g. arterial phase) and ilium (h. arterial phase) shrunk significantly. The right branch of portal vein was released by tumor (b. portal vein phase), and necrotic tumor was absorbed generally (c. arterial phase).

**Figure 6**

The change trend of AFP and PIVAK-II. AFP reduced to normal since August 05, 2022, and PIVAK-II was found below the reference range on January 06, 2023.