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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

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CASE REPORT

Pathologic complete response to conversion therapy in hepatocellular carcinoma using patient-derived organoids: A case report

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Abstract

BACKGROUND

For primary liver cancer, the key to conversion therapy depends on the effectiveness of drug treatment. Patient-derived tumor organoids have been demonstrated to improve the efficacy of conversion therapy by identifying individual-targeted effective drugs, but their clinical effects in liver cancer remain unknown.

CASE SUMMARY

We described a patient with hepatocellular carcinoma (HCC) who achieved pathologic complete response (pCR) to conversion therapy guided by the patient-derived organoid (PDO) drug sensitivity testing. Despite insufficiency of the remaining liver volume after hepatectomy, the patient obtained tumor reduction after treatment with the PDO-sensitive drugs and successfully underwent radical surgical resection. Postoperatively, pCR was observed.

CONCLUSION

PDOs contributes to screening sensitive drugs for HCC patients to realize the personalized treatment and improve the conversion therapy efficacy.

Key Words: Tumor organoids; Hepatocellular carcinoma; Drug sensitivity testing; Conversion therapy; Pathological response; Case report

Core Tip: Patient-derived tumor organoids have been demonstrated to improve the efficacy of conversion therapy by identifying individual-targeted effective drugs. Here we described a patient with hepatocellular carcinoma (HCC) who achieved pathologic complete response to conversion therapy guided by the patient-derived organoid (PDO) drug sensitivity testing. This typical case suggests that PDO-based drug sensitivity testing contributes to screening sensitive drugs for HCC patients to realize the personalized treatment and to improve the efficacy of conversion therapy, which may change the previous experiential therapy and serve as a novel treatment mode in liver cancer.

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INTRODUCTION

Primary liver cancer (PLC) is a common malignant tumor in the digestive system, and the treatment modalities for PLC include hepatectomy, liver transplantation, ablation therapy, transarterial chemoembolisation (TACE), radiation therapy, systemic anti-tumor therapy, and more. At present, radical surgical resection remains the only completely cured method for PLC[1,2]. Selection of appropriate treatment methods for liver cancer patients at different stages can maximize the therapeutic effect[3]. Conversion therapy is an effective technique for patients with advanced liver cancer to achieve radical resection and long-term survival, which can transform the liver cancer with poor oncological characteristics into that with good oncological characteristics, thereby reducing postoperative recurrence and prolonging the survival[4,5]. Currently, the most common conversion therapies for liver cancer include systemic anti-tumor therapy, local therapy, and radiotherapy[4]. However, one of the key issues that urgently need to be solved is the selection of conversion therapy regimens. Current treatment mainly depends on traditional experience or clinical trial results. On the one hand, an effective treatment regimen for most patients may be ineffective for a certain case at the individual level. On the other hand, how to choose the most effective regimen among the various options is a core concern of conversion therapy.

Tumor organoids, a kind of three-dimensional (3D) microstructures formed by *in vitro* culture of tumor tissues from patients under a highly similar condition to the human microenvironment, can maintain the biological behaviors and functions of original tumors while retaining pathohistological and genetic features, which provide an effective platform for tumor research and drug discovery[6,7]. Unlike patient-derived xenografts, patient-derived organoids (PDOs) require less time and tissue for establishment and can faithfully recapitulate the key characteristics of original tumors even after long-term passaging[8]. By comparing responses to antitumor agents from PDOs and PDO-based xenograft models with those of patients in clinical trials, Vlachogiannis *et al*[9] demonstrated that PDOs effectively retained the patients' clinical response and could be used in precision medicine protocols. Importantly, the PDOs can be co-cultured with immune cells, cancer-associated fibroblasts and vasculatures to model the tumor microenvironment (TME), thereby allowing for more effective screening of personalized drugs[10].

Currently, organoid-based drug sensitivity testing is gradually being applied in various scenarios, including neoadjuvant and/or palliative chemotherapy, ineffective first-line treatment, advanced and rare cancers, *etc*[11]. Here, we reported a patient with hepatocellular carcinoma (HCC) who achieved pathologic complete response (pCR) to conversion therapy under the guidance of the PDO-based drug sensitivity testing.

CASE PRESENTATION

Chief complaints

A 55-year-old woman was admitted to hospital because of abdominal pain and fever for 10 days.

History of present illness

The patient had abdominal pain and fever for 10 days.

History of past illness

The patient previously received multiple surgeries, including choledochocystectomy, biliary-enteric anastomosis and cholecystectomy for congenital choledochal cysts, as well as left lateral hepatic lobectomy and bile duct exploration for left intrahepatic bile duct stones.

Personal and family history

The patient denied any family history of malignant tumors.

Laboratory examinations

Laboratory examinations included: Carbohydrate antigen (CA) 19-9 of 49.09 U/mL, CA125 of 83.8 U/mL, alpha fetoprotein of 1.64 ng/mL, carcinoembryonic antigen of 1.3 ng/mL, and CA15-3 of 8.5 U/mL (Table 1).

Imaging examinations

The computed tomography (CT) scan showed a slightly low-density mass shadow in the right lobe of the liver, suggesting the possibility of tumors or metastatic lesions (Figure 1A-C). Positron emission tomography/CT further indicated a liver tumor without distant metastasis.

FINAL DIAGNOSIS

In combination with relevant examinations and previous history of surgery, it was speculated that the tumor was located in the right posterior lobe of the liver, with a diameter of 9.0 cm × 6.4 cm. After multi-disciplinary team (MDT) discussion, a needle biopsy was performed, and HCC was confirmed (Figure 2).

TREATMENT

After the patient and her family members were informed consent, tumor tissues from needle biopsies were collected for organoid culture. First, the tumor tissues were rinsed using precooled phosphate-buffered saline, and then minced. Second, cell pellets were collected through centrifugation following 30-minute digestion. When Matrigel was added, cells and Matrigel suspension were both seeded onto 6-well plates (2 mL per well) using pipettes, and the plates were placed in a 37 °C incubator for 15 minutes. Third, the culture medium [Kingbio Medical (Chongqing) Co., Ltd., China] was supplemented after the droplets were fully solidified, and the plates were again placed into an incubator (37 °C, 5% CO_2) for culture. Notably, the culture medium was replaced every 2-3 days. Subsequently, the organoids conforming to requirements were seeded in 96-well plates, with corresponding drugs added. There were at least 3 compound pores. Meanwhile, a negative control was set up[12]. Finally, the organoid activity values were read using a multimode reader after treatment with drugs, and the drug sensitivity was calculated.

During organoid culture, TACE with lobaplatin (50 mg) was used as the initial treatment option in combination with Lenvatinib (40 mg/d) and tislelizumab (200 mg per time, once every three weeks). However, the increased levels of tumor markers CA19-9 and CA125 were observed after treatment (Table 1). Based on the organoid drug sensitivity testing, we found that the PDO was more sensitive to doxorubicin compared with other agents (Figure 3), thus lobaplatin was replaced by doxorubicin in TACE, but the usage and dosage of Lenvatinib and tislelizumab were unchanged. After two cycles of treatment, the levels of tumor markers CA19-9 and CA125 were decreased significantly (Table 1). CT and magnetic resonance imaging examinitions both showed a signifcantly reduced tumor diameter in the liver (Figure 1D-I), which was assessed resectable according to Response Evaluation Criteria in Solid Tumors (version 1.1). In addition, the liver functional reserve indicators of the patient were also improved. Prior to neoadjuvant therapy, the patient had Child-Pugh B, indocyanine green retention rate at 15 minutes (ICG-R15) of 15% and China liver cancer staging of Ib. After neoadjuvant therapy, the patient was assessed as Child-Pugh A and ICG-R15 of 8.3%.

Through MDT discussion, the sufficient remaining liver volume was calculated after lesion resection. Subsequently, right posterior hepatic lobectomy and partial phrenectomy were performed following communication with the patient. The time interval between the last preoperative TACE and surgery was 4 weeks. Postoperative pathology suggested partial liver cell edema, chronic inflammation in the portal area, fibrous hyperplasia, and focal deposition of hemosiderin, without definite residual cancer tissues and cancer cells in the cutting edge, suggesting pCR.

OUTCOME AND FOLLOW-UP

The patient attended our hospital for further consultation 7 months after surgery, and no recurrence or metastasis was observed based on CT examinations (Figure 1J-L).

DISCUSSION

The PLC originating from the epithelial or mesenchymal tissues of the liver is one of the most common malignancies, of which HCC accounts for 75%-85%[13]. Currently, radical surgery remains the main treatment modality for liver cancer patients to achieve long-term survival[3]. However, most liver cancer patients are initially diagnosed at the middle and advanced stage, inappropriate for surgical resection. Although some patients have undergone surgery, the risk of postoperative recurrence and metastasis is high.

Conversion therapy aims to converting unresectable liver cancer into resectable liver cancer to remove the tumor, which is one of the most promising ways to perform radical surgery and improve the long-term survival of patients with liver cancer[4]. At present, use multimodal and high-intensity anti-tumor therapies is recommended to promote the

Table 1 Changes of tumor markers at different time points

Indicators	AFP (ng/mL)	CA19-9 (U/mL)	CEA (ng/mL)	CA125 (U/mL)	CA15-3 (U/mL)
On admission	1.64	49.09	1.30	83.80	8.50
After the initial treatment	2.07	55.00	1.66	91.00	9.00
After organoid-based treatment	2.45	25.67	1.21	34.20	10.20
7 months after surgery	2.37	27.41	1.36	23.95	10.60

AFP: Alpha fetal protein; CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen.

conversion of the PLC, with consideration of the treatment safety[5]. The commonly used anti-tumor treatment modalities for liver cancer include TACE, targeted therapy, immunotherapy, radiotherapy, or a combination of multiple therapies, among which chemotherapy mainly focusing on liver tumor perfusion/embolization and targeted therapy are one of the most important methods for liver tumor conversion. However, there is still a lack of precise methods regarding the selection of specific drugs for liver tumors. The selection strategy of each center is to choose the most effective plan based on guidelines or clinical experience, or to choose a new plan based on the latest clinical research. Notably, there exist several problems. First, the most effective plan, as proven by experience, may be effective for most cases, but may be inefficient or even ineffective in some patients. Second, for individual cases, there may be several effective chemotherapy or targeted regimens available simultaneously. At present, choosing the most effective regimen to achieve the optimal conversion efficiency is still difficult.

In recent years, the emergence of 3D culture technology represented by PDOs has opened up a new method for studying tumor evolution and evaluating treatment response. For liver cancer, several major subtypes of organoids have been successfully established, including HCC, cholangiocarcinoma, biliary tract cancer, etc. However, the success rate of generating liver cancer organoids is only about 30%[14], significantly lower than 75%-85% for pancreatic cancer organoids[15] and 90% for colorectal cancer organoids[16], which may partially be explained by epithelial-mesenchymal transition and limited HCC subpopulations. In our study, HCC organoids from needle biopsies were successfully generated, supported by the data from the study by Nuciforo *et al*[14].

Currently, liver cancer organoids have been demonstrated not only to retain the histological and molecular features of original tumors, but also help identify the drug sensitivity of individual patients[17]. Saltsman *et al*[18] presented the potential of hepatoblastoma organoids in improving treatment options for a subset of hepatoblastoma patients irresponsive to existing treatments. Additionally, based on pharmaco-proteogenomic profiling of the liver cancer organoids, Ji *et al*[19] identified potential drug combination therapies, thus offering guidance for clinical patient selection and drug combination therapies. Although a strong association between use of PDOs and clinical outcomes in predicting chemotherapy and/or radiotherapy efficacy has been confirmed in multiple cancer types[9,20,21], there is lack of evidence in HCC, especially in use of PDOs to guide conversion therapy. In our study, the initial treatment of TACE with lobaplatin in combination with tislelizumab and Lenvatinib did not yield satisfactory therapeutic effects. According to organoid drug sensitivity testing results, one of the chemotherapy drugs during TACE was adjusted to doxorubicin, with unchanged usage and dosage of Lenvatinib and tislelizumab. After treatment, tumor markers returned to normal, and the tumor significantly reduced. The patient achieved pCR after radical resection, and no recurrence or metastasis was observed 7 months after surgery. Collectively, the organoid drug sensitivity testing helps to screen suitable chemotherapy drugs for liver cancer patients, thereby promoting conversion therapy.

Notably, surgical safety should be considered for HCC patients successfully achieving conversion therapy. However, for different preoperative treatments the timing of surgical resection is different. It is reported that continuous use of small molecule drugs, such as tyrosine kinase inhibitors, cannot increase the incidence of postoperative complications [22]. If conversion therapy based on immune checkpoint inhibitors is applied for HCC preoperatively, surgery should be performed within 4 weeks after the last dose[23]. If adverse reactions occur during neoadjuvant therapy, surgery will be performed after drug withdrawal until grade I or no adverse reactions[24]. Additionally, TACE-based neoadjuvant therapy can cause liver inflammation, increase the amount of intraoperative bleeding and the difficulty of surgical procedures. It is recommended in Chinese expert consensus on conversion and perioperative therapy of PLC that the interval between the last preoperative TACE and surgery should be greater than 4 weeks[24]. In our case, the duration between the preoperative last TACE and surgery was just 4 weeks.

To the best of our knowledge, this is the first case to select the most effective regimen to promote conversion therapy using the PDO model and the first case to transform empirical modes into precision modes. During organoid culture, traditional empirical models including TACE plus targeted therapy were first used. Three weeks later, precise treatment was employed based on the organoid drug sensitivity results, and pCR was obtained. Notably, there are still some challenges in the use of PDOs in clinical practice, including sample availability and processing, standardization of culture protocols, turnaround time and scalability, recapitulation of the TME, optimization of culture medium, *etc*[11]. With technical development and continuous research, the combination of the PDOs with other advanced technologies, such as organ-on-a-chip, 3D bioprinting and CRISPR-HOT, allows for modeling more complicated and realistic state, which may help to overcome the above challenges and create more appropriate model systems for cancer treatment.

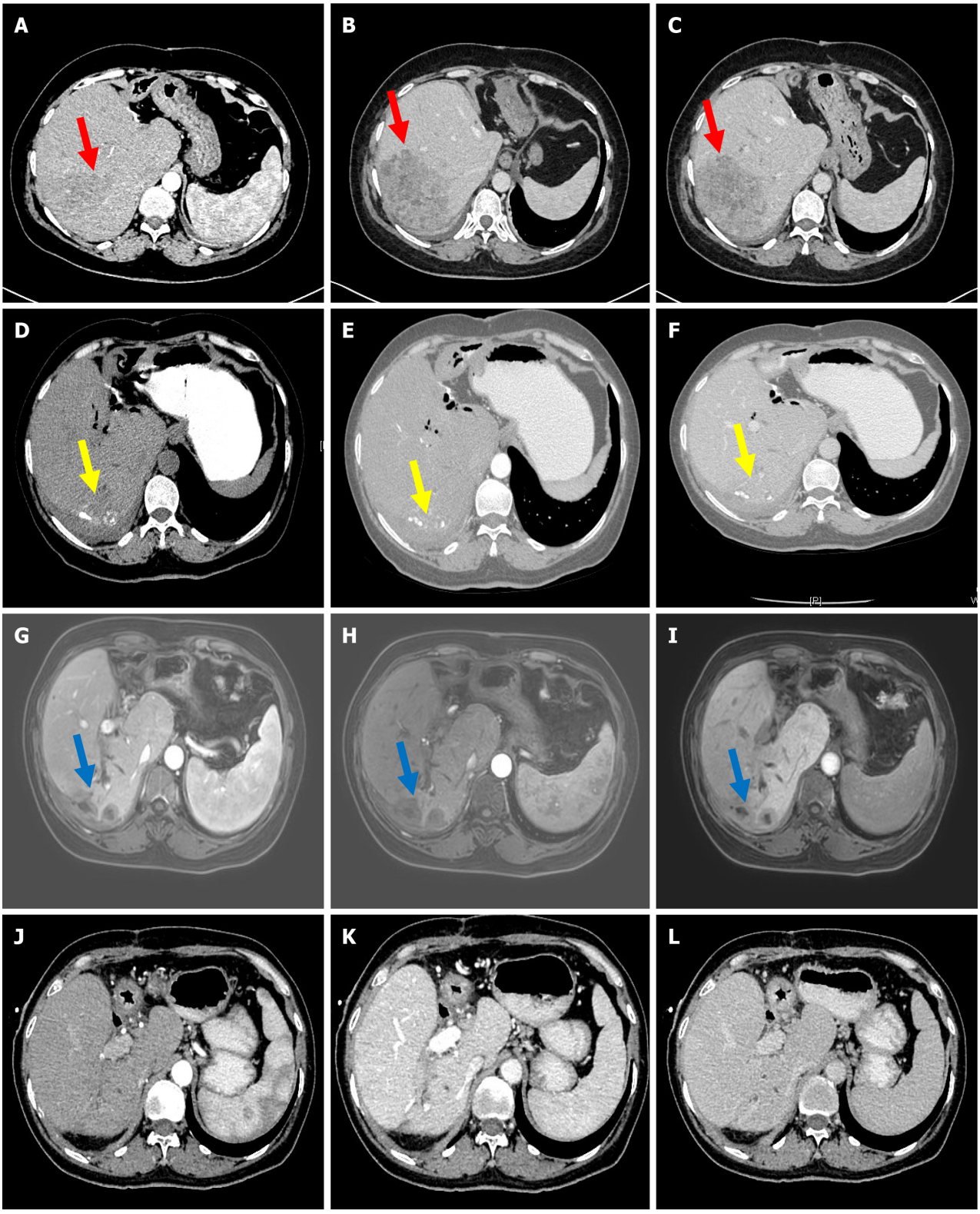

Figure 1 Radiological images of the patient before and after conversion therapy. A-C: computed tomography (CT) examination shows that the tumor is in the right lobe of the liver before conversion therapy; D-F: CT and magnetic resonance imaging; G-I: Examinations both indicate a decreased tumor in the right lobe of the liver before surgery; J-L: Seven months after surgery, no recurrence or metastasis was observed under the CT. The red, yellow, and blue arrows all head towards the tumor.

CONCLUSION

PDO-based drug sensitivity testing contributes to screening sensitive drugs for HCC patients to realize personalized treatment and to improve the effectiveness of conversion therapy, which may change the previous experiential therapy and become a novel treatment mode in liver cancer.

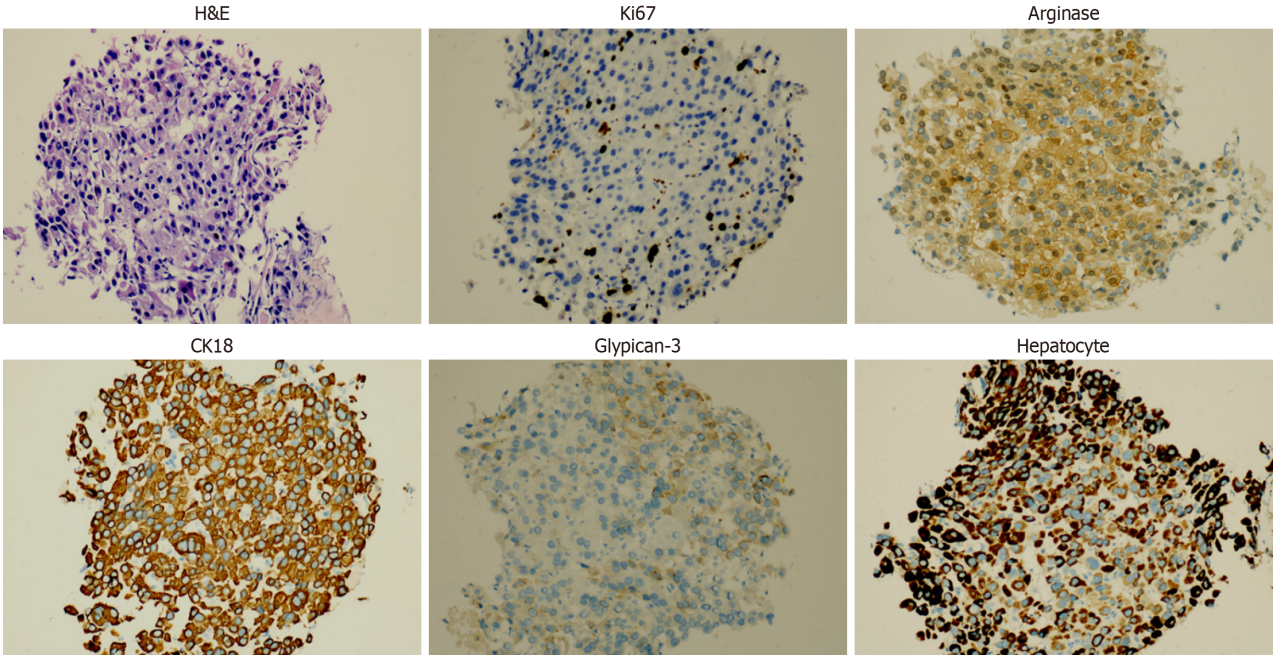

Figure 2 Images of HE and immunohistochemical staining of the biopsy specimen (× 200).

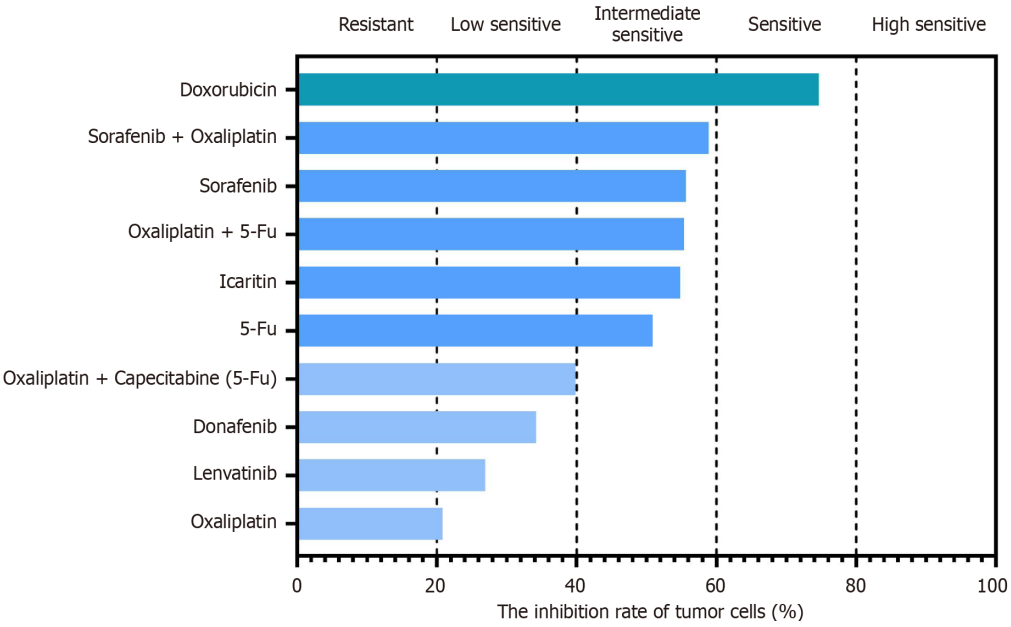

Figure 3 The drug sensitivity results of the patient-derived organoid from hepatocellular carcinoma.

FOOTNOTES

Author contributions: He YG, Li J and Wang Z were responsible for writing the first draft; Xi W and Zhao CY participated in data acquisition and investigation. Supervision was performed by Huang XB and Zheng L. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All the authors contributed to the study conception and design. He YG and Wang Z contributed equally to this work as co-first authors.

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