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ORIGINAL ARTICLE

MiniPDX-guided postoperative anticancer treatment can effectively prolong the survival of patients with hepatocellular carcinoma

Long Yang[1,2] · Zheyue Yuan[2] · Yamin Zhang[2] · Zilin Cui[2] · Yang Li[2] · Jiancun Hou[2] · Xiaolong Liu[2] · Zirong Liu[2] · Rui Shi[2] · Qing Tian[2] · Jian Wang[2] · Lianjiang Wang[2]

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Abstract

Background The recurrence rate of hepatocellular carcinoma (HCC) after partial hepatectomy is still high. How to choose the most appropriate anti-tumor drug in the early postoperative period is crucial to improve the prognosis of patients. Recently, MiniPDX has been widely used as a new and reliable preclinical research model capable of predicting the sensitivities of anti-tumor drugs.

Methods Twenty-eight patients with HCC were selected to use the MiniPDX model to screen the most sensitive anti-tumor drugs from five groups of drug regimens for preventive treatment after partial hepatectomy, and another 42 patients with HCC were selected to be treated with Sorafenib during the same period as the control group. The tumor-free survival rate and overall survival rate were analyzed and compared between these two groups. The relationship between drug sensitivity and biomarkers related to HCC was also analyzed.

Results Kaplan–Meier survival curve analysis showed that the tumor-free survival (DFS) of patients in the MiniPDX group was significantly longer than that in the control group (median DFS: 25.8 months vs. 18.2 months, $P=0.022$, HR 2.19, 95% CI 1.17–4.12). The overall survival (OS) of the patients in the MiniPDX group was also longer than that in the control group (median OS: 29.4 months vs. 23.8 months, $P=0.039$, HR 2.37, 95% CI 1.12–5.00). The longest follow-up period was 36 months. The relationship analyzed between the efficacy of the five drugs (Regorafenib, Regorafenib, Lenvatinib, Gemcitabine, 5-FU + Oxaliplatin) and AFP, Ki-67, VEGFR, FGFR, P53, and Nrf2 showed different correlations.

Conclusion The use of the MiniPDX model to select drugs to guide anti-tumor treatment after partial hepatectomy could effectively prolong the survival of patients with HCC.

Keywords Hepatocellular carcinoma · MiniPDX · Targeted drugs · Chemotherapy · Survival

Introduction

Primary liver cancer is one of the most common malignant tumors, ranking sixth in the incidence of malignant tumors worldwide and second in the cause of tumor death [1]. Approximately 90% cases of primary liver cancer cases are hepatocellular carcinoma (HCC), and liver resection is currently the preferred treatment. However, because of the high malignancy of HCC, the recurrence rate is still high after radical resection. According to statistics, the 5-year recurrence rate of patients with HCC after partial liver resection is as high as 70% [2]. Therefore, it is crucial to develop ways to reduce postoperative tumor recurrence and improve the long-term prognosis of patients.

Postoperative application of targeted drugs and systemic chemotherapy to prevent HCC recurrence are a few proven options, but because of the multiple drug resistance, the use of single drugs has limited therapeutic effect. There are currently no precise indicators or plans for individualized medication guidance. It is therefore important to determine how to accurately select effective drugs and develop individualized treatment plans. In recent years, scholars have attempted to screen anti-tumor drugs in vitro by simulating tumors. The human-derived tumor xenograft model

✉ Yamin Zhang
13802122219@163.com

[1] Medical School of Nankai University, No. 94, Weijin Road, Nankai District, Tianjin, China

[2] Department of Hepatobiliary Surgery, Tianjin First Central Hospital, School of Medicine, Nankai University, No. 24 Fukang Road, Nankai District, Tianjin, China

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(Patient-Derived-Xenograft, PDX) has emerged in this context and has achieved certain clinical results.

PDX is currently the most representative animal model of human tumor genetic information [3]. It is different from the traditional cell line xenograft model and genetically engineered mouse model because the patient's tumor tissue is directly used to establish a subcutaneous xenograft model, which can better retain the special functional gene structure and biomarkers of the tumor in the individual, closer to the clinical biological characteristics of tumors in patients. It retains the growth characteristics of tumors in the human body, thus acting as an "in vivo laboratory" similar to patients' own tumors [4]. Thus, it can provide accurate predictions for the screening of anti-tumor drugs and observation of their efficacy. According to reports, the accuracy of PDX samples for drug effectiveness and drug resistance rates can reach 90% [5].

Although the PDX drug sensitivity test has obvious advantages, from the establishment of the model to the drug sensitivity test of traditional PDX, it needs to go through the process of modeling, passage, amplification, and efficacy analysis, which takes approximately 4–7 months. In clinical practice, patients with HCC have a limited treatment window after surgery. Secondly, the tumor formation rate of the traditional PDX model is affected by tumor types, tissue ex vivo time, and the type of rat modeled, which leads to the instability of the PDX tumor formation rate, especially for HCC, that varies between 13 and 90% [6].

The latest rapid, human-derived xenograft tumor susceptibility detection technology (MiniPDX) solves this problem very well. This technology uses in vitro isolation of primary tumor cells from tumor specimens and in vivo drug sensitivity tests. Primary tumor cells isolated from tumor tissue are placed in a special, semi-permeable membrane device, implanted in mice, and then compared with a clinical administration route (oral gavage, intravenous injection or intraperitoneal injection) for comparative research. Finally, the device is removed for cell viability test, and drug sensitivity results are obtained based on the strength of the viability and tumor cell proliferation; the drug sensitivity test cycle takes only 2 weeks [7], Clinical studies have confirmed that MiniPDX can help improve the prognosis of patients with gallbladder cancer [8].

Therefore, in this study, MiniPDX was used to test the specimens of patients with HCC to screen the best postoperative anti-tumor drugs for these patients. We used MiniPDX to guide the postoperative anti-tumor treatment of 28 patients with HCC. We selected the most effective single-agent preventive treatment from three targeted drugs and two cytotoxic drugs to assess whether these drugs can effectively reduce tumor recurrence and prolong survival time. We also analyze the relationship between the sensitivity of each drug and the expression of biomarkers.

Materials and methods

Inclusion criteria

All cases in this study were patients with HCC who underwent liver resection at Tianjin First Central Hospital from December 2016 to December 2019. Patients who met the following criteria at the start of treatment were eligible for the study:

(1) Over 18 years old and under 70 years old. (2) Patients with primary liver cancer diagnosed before surgery and radical resection was feasible. (3) The indication for operation may be for benign or malignant disease. (4) No large vessel invasion and no extrahepatic lymph nodes and extrahepatic organ metastasis. (5) The expected survival period was greater than 3 months. (6) Patients who can understand the purpose of this study, take the test voluntarily, and complete the informed consent sign.

Grouping and specimen acquisition

We introduced the MiniPDX treatment plan to the subjects in detail. According to the patients' treatment wishes, 28 patients were screened for anti-tumor drugs by the MiniPDX model and included in the experimental group, namely the MiniPDX group. During the same period, 42 patients with HCC who did not undergo the MiniPDX test were included in the control group; patients in this group were treated with regular medications. In the MiniPDX group, $10\times10\times5$ mm^3 cancer tissues were excised during the operation and stored in a preservation solution for examination.

Test animals

Nu mice were housed at the SPF animal room IVC under a constant temperature and constant pressure system at LIDE Biotech (Shanghai, China). CB17-SCID mice were used for MiniPDX model recovery and nu mice were used for drug efficacy tests. All study protocols were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) at LIDE Biotech and conducted in accordance with established national and international regulations for laboratory animal protection.

MiniPDX model establishment

Tumors ≥ 500 mm^3 in size with a necrotic area of $<30\%$ were used. The protocol was followed and described below: (1) Sample preparation: briefly, tumor tissues were washed with Hank's balanced salt solution (HBSS) to remove nontumor tissues and necrotic tumor tissue in a biosafety cabinet. (2)

Sample digestion: after the tumor tissues were morselized, they were digested with collagenase at 37 °C for 1–4 h with the digest enzyme from OncoVee® MiniPDX Assay Kit. (3) Cells isolation: cells were pelleted by centrifugation at 600 g for 5 min followed by the removal of blood cells and fibroblasts with magnetic beads. (4) Capsules preparation: cells were then filled into OncoVee® capsules. (5) Capsules implantation: capsules were implanted subcutaneously via a small skin incision with three capsules per mouse (5-week-old nu/nu mouse), two mice per drug regimen [7]. The MiniPDX flowchart is shown in Fig. 1.

Drug sensitivity test

Mice bearing MiniPDX capsules were treated with drugs or their combinations as detailed in Table 1 for 7 days. Thereafter, the implanted capsules were removed, and tumor cell proliferation was evaluated using the CellTiter Glo Luminescent Cell Viability Assay kit, as instructed by the manufacturer. Luminescence was measured in terms of relative luminance unit (RLU) using a spectrophotometer. Relative proliferation rate (RPR) was calculated using the following equation: (Mean RLU of the treatment group on day 7 − Mean RLU on day 0)/(Mean RLU of the vehicle group on day 7 − Mean RLU on day 0) × 100%.

Each experiment was conducted in sextuplicate, and mean values were reported. A positive drug response was considered present if RPR was ≦ 55%, and a negative drug response was considered if RPR was > 55%.

Postoperative anti-tumor therapy

The experimental group started treatment with anti-tumor drugs screened by MiniPDX 2 weeks after partial hepatectomy. The treatment was discontinued if poor tolerance or serious adverse reactions occurred. Adverse events occurred were recorded. The control group empirically used sorafenib for anti-tumor treatment.

Follow-up

Follow-ups were conducted once every month during the first half-year post operation and once every 3 months thereafter. Phone calls were made to patients or their relatives. OS was calculated from the date of surgery until the date of the final follow-up visit or death, and DFS was calculated from the date of surgery until the final follow-up visit or tumor recurrence. The final follow-up visit was December 2019.

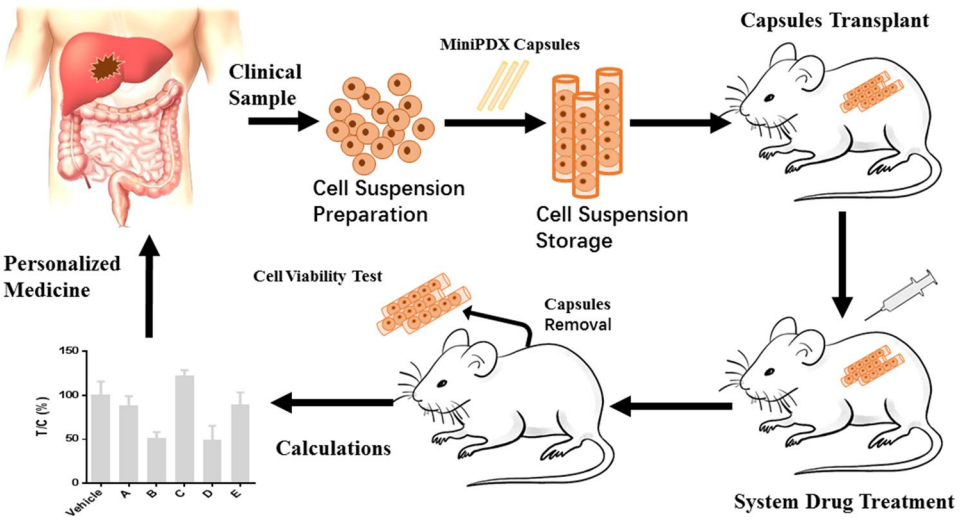

Fig. 1 Schematic of MiniPDX modeling and drug sensitivity detection

Table 1 Drug preparations and treatment details

Drug	Supplier	Preparation	MiniPDX assay
Sorafenib	Meilun Bio	1:1 Castor Oil & Absolute Ethanol	40mpk,po,qd*7
Regorafenib	Bide Pharma	0.5%HPMC + 0.2%TWEEN 80	30mpk,po,qd*7
Lenvatinib mesylate	Bide Pharma	0.5%HPMC + 0.2%TWEEN 80	100mpk,po,qd*7
Gemcitabine	Aosaikang Pharma	0.9% NaCl Solution	60mpk,ip,q4d*2
5-FU	Bide Pharma	0.9% NaCl Solution	25mpk,ip,qd*5
Oxaliplatin	Qilu Parma	5% Glucose	5mpk,ip,q4d*2

Biomarker immunohistochemical staining

Tissue sections were dewaxed and rehydrated. Antigen retrieval was performed by incubating the slides in 0.01 M citric acid buffer at 100 °C for 10 min. After blocking with 3% H_2O_2 and 5% fetal bovine serum, the slides were allowed to react with antibody against AFP(ab169552, Abcam), Ki-67(ab15580, Abcam), VEGFR(ab233693, Abcam), FGFR(ab76464, Abcam), p53(ab179477, Abcam), and Nrf2(ab62352, Abcam) at a dilution of 1:200 in 5% fetal bovine serum at 4 °C overnight. The slides were then incubated with polymer-HRP reagent (BioGenex, San Ramon, CA). The peroxidase activity was visualized with diaminobenzidine tetrahydroxychloride solution (DAB, BioGenex). Immunohistochemical staining was semi-quantitatively scored by rating staining intensity of a protein of interest (*I*: negative, 0; weak, 1; moderate, 2; intense, 3) and the percentage of positively stained cells (*P*: 0–5%, scored 0; 6–25%, scored 1; 26–50%, scored 2; 51–75%, scored 3; and > 75%, scored 4) to obtain a final score (*Q*), which was defined as the product of $I \times P$. $Q > 5$ was defined as high expression.

Statistical analysis

Normally distributed continuous variables were analyzed using unpaired Student's *t* test. Chi-square test was used for baseline characteristics data. The Kaplan–Meier method and the log-rank test were used to analyze OS and DFS. SPSS 21 software was used for all statistical analyses. For all analyses, $P < 0.05$ was considered statistically significant.

Ethical approval

The present study was approved by the Ethical Review Committee of China Registered Clinical Trial (no.ChiECRCT20190201). All animal tests were approved by the Institutional Animal Care and Use Committee (no.LDIACUC001). Written informed consents were provided by all participants before enrollment. All procedures were performed in accordance with the Ethical Standards of Institutional/National Research Committees and the 1964 Helsinki Declaration, its later amendments, or similar ethical standards.

Results

Characteristics of the patients

There were no significant differences in gender, age, basal liver disease, alpha-fetoprotein, tumor size, degree of differentiation, staging, and surgical approach between the two groups of patients (Table 2).

MiniPDX drug sensitivity test results

The cell viability test for the MiniPDX model in 28 patients with HCC showed that the relative proliferation rate of cancer cells using sorafenib, regorafenib, lenvatinib, gemcitabine, and 5Fu + oxaliplatin was 66.25 ± 27.93%, 79.25 ± 21.09%, 59.82 ± 25.83%, 61.68 ± 29.89%, and 58.39 ± 30.38%, respectively (Fig. 2). The relative proliferation rate of ≦ 55% was considered to be effective, and the effective rates of the five groups of drugs were 32.14, 10.71, 39.29, 50.00, and 46.43%, respectively.

Follow-up results of two groups

The longest follow-up time for this study was 36 months. Kaplan–Meier survival curve analysis showed that the tumor-free survival (DFS) of patients in the MiniPDX group was significantly longer than that in the control group (median DFS: 25.8 months vs. 18.2 months, $P = 0.022$, HR 2.19, 95% CI 1.17–4.12). The overall survival (OS) of patients in the MiniPDX group was also longer than that of the control group (median OS: 29.4 months vs. 23.8 months, $P = 0.039$, HR 2.37, 95% CI 1.12–5.00) (Fig. 3).

Relationship between drug sensitivity and biomarkers

Figure 4 shows the differences in the expression of biomarkers in different HCC patients. We analyzed the relationship between the relative increase rate of tumor cells of five groups of drugs detected by the MiniPDX model and the expression of biomarkers in patients and found that sorafenib and lenvatinib have stronger antitumor effects in patients with high expression of VEGFR. The efficacy of both these drugs was significant (Fig. 5c). Patients with high FGFR expression were more sensitive to regorafenib and lenvatinib (Fig. 5d), while patients with high P53 expression show resistance to cytotoxic drugs to a certain extent (Fig. 5e) The 5Fu + oxaliplatin group showed a stronger cytotoxic effect on HCC cells with low Nrf2 expression (Fig. 5f).

Discussion

In recent years, reducing the recurrence rate of HCC after partial hepatectomy has become a hot topic. Some scholars have attempted to treat patients with HCC with systemic

Table 2 Baseline characteristics

Characteristic	All	Control group	MiniPDX group	OR (95%CI)	χ^2	*P*
NO	70	42	28			
Gender (M/F), *n* (%)	46 (65.7)/24 (34.3)	24 (57.1)/18 (42.9)	22 (78.6)/6 (21.4)	0.364 (0.122–1.082)	3.424	0.064
Age, years, *n* (%)						
≤60	34(48.6)	19(45.2)	15(53.6)	0.716 (0.274–1.869)	0.467	0.494
HBsAg, *n* (%)						
Positive	56 (80.0)	32 (76.2)	24 (85.7)	0.533 (0.149–1.908)	0.952	0.329
Cirrhosis, *n* (%)						
Yes	56 (80.0)	33 (78.6)	23 (82.1)	0.797 (0.236–2.689)	0.134	0.714
Child Pugh, *n* (%)						
A	57 (81.4)	34 (81.0)	23 (82.1)	0.924 (0.268–3.181)	0.016	0.900
B	13 (18.6)	8 (19.0)	5 (17.9)			
Alpha-foetoprotein, U/ml, *n* (%)						
<400	51 (72.9)	31 (73.8)	20 (71.4)	1.127 (0.387–3.287)	0.048	0.826
≥400	19 (27.1)	11 (26.2)	8 (28.6)			
Tumor number, *n* (%)						
1	59 (84.3)	36 (85.7)	23 (82.1)	1.304 (0.357–4.772)	0.004	0.947
≥2	11 (15.7)	6 (14.3)	5 (17.9)			
Tumor size, cm, *n* (%)						
≤5	34 (48.6)	20 (47.6)	14 (50.0)	0.909 (0.349–2.367)	0.038	0.845
Operation way, *n* (%)						
Anatomical hepatectomy	52(74.3)	30(71.4)	22(78.6)	0.682(0.222–2.098)	0.449	0.503
Nonanatomical hepatectomy	18(25.7)	12(28.6)	6(21.4)			
Blood loss, ml, *n* (%)						
≤200	42 (60.0)	24 (57.1)	18 (42.9)	0.741 (0.277–1.984)	0.357	0.550
Tumor differentiation, *n* (%)						
Well and moderate	50 (71.4)	28 (66.7)	22 (78.6)	0.545 (0.180–1.651)	1.167	0.280
Microvascular invasion, *n* (%)						
Yes	18 (25.7)	13 (31.0)	5 (17.9)	2.062 (0.642–6.628)	1.508	0.219

Chi-square test

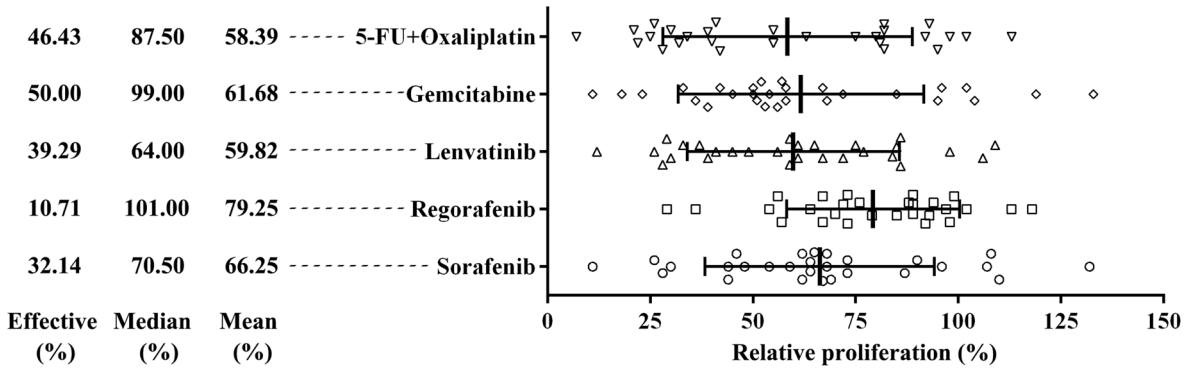

Fig. 2 The scatter plot of the relative appreciation rate of the five groups of drugs by MiniPDX, and the effectiveness of each group of drugs (relative proliferation rate ≤ 55% is effective)

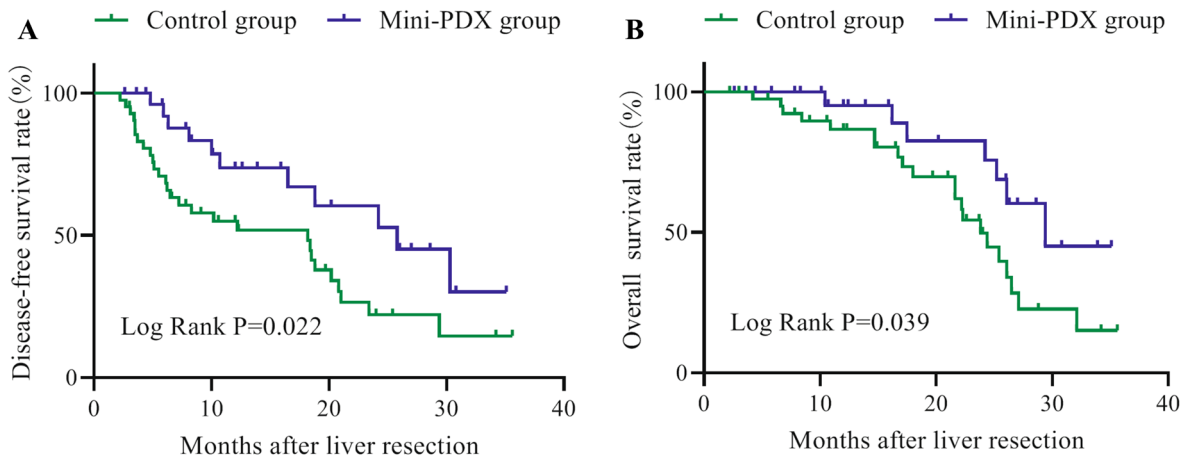

Fig. 3 Kaplan–Meier survival curves of the two groups of patients. **a** The tumor-free survival rate of patients in the MiniPDX group was significantly higher than that in the control group. **b** The overall survival rate of patients in the MiniPDX group was significantly higher than that in the control group. Two groups of data were analyzed by log-rank test

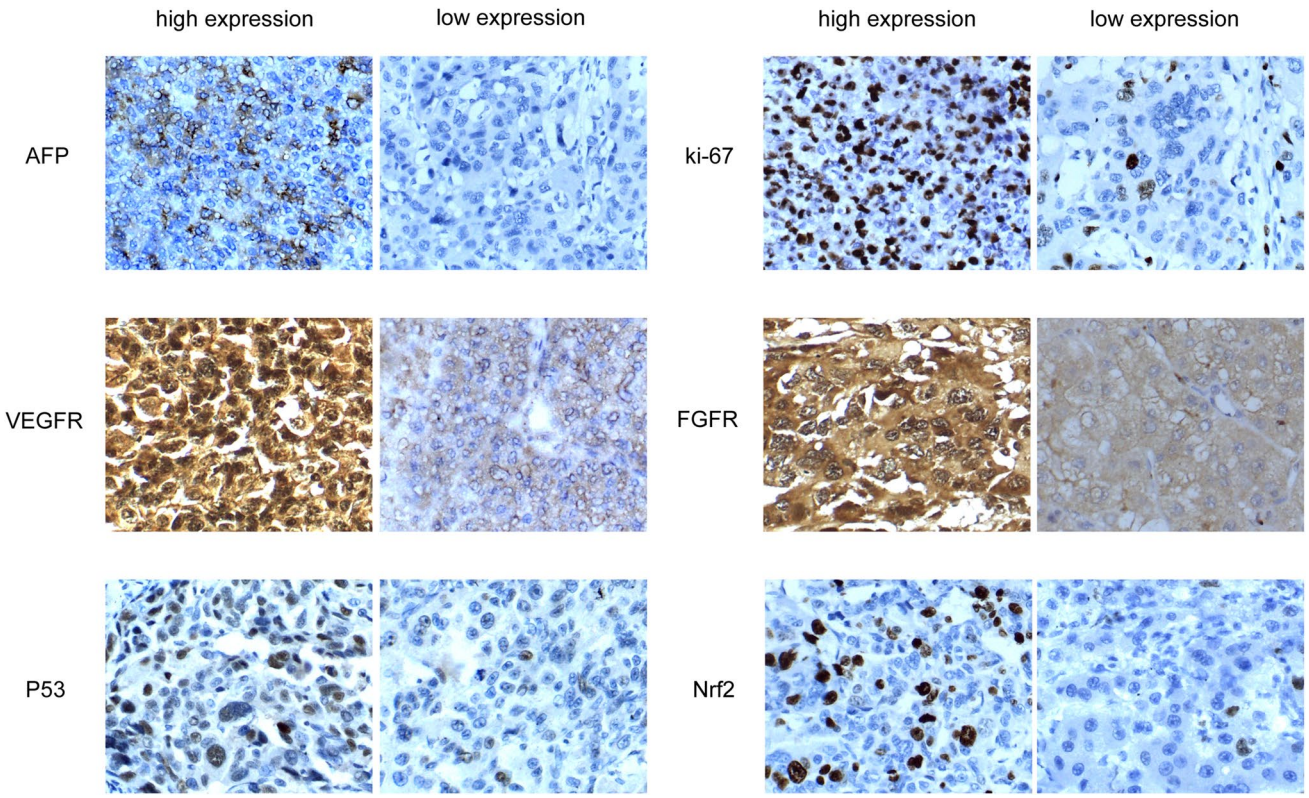

Fig. 4 Representative high and low expression of 6 biomarkers(AFP, ki-67, VEGFR, FGFR, P53, and Nrf2) in HCC tissue studied by immunohistochemistry (×200)

cytotoxic drugs such as doxorubicin, capecitabine, platinum and 5-fluorouracil (5-Fu) after the surgery, with an aim to reduce the recurrence rate.[9, 10]. However, because of the existence of multidrug resistance (MDR) and the heterogeneities of HCC, the effective rates of single cytotoxic drugs are generally lower than 20%, which leads to decline in patient life quality. In recent years, with increasing advancements in genomics and the next generation sequencing, targeted drug therapy for the treatment of advanced HCC has gradually been recognized. Sorafenib was the earliest drug approved by Food and Drug Administration (FDA) for the treatment of advanced HCC.

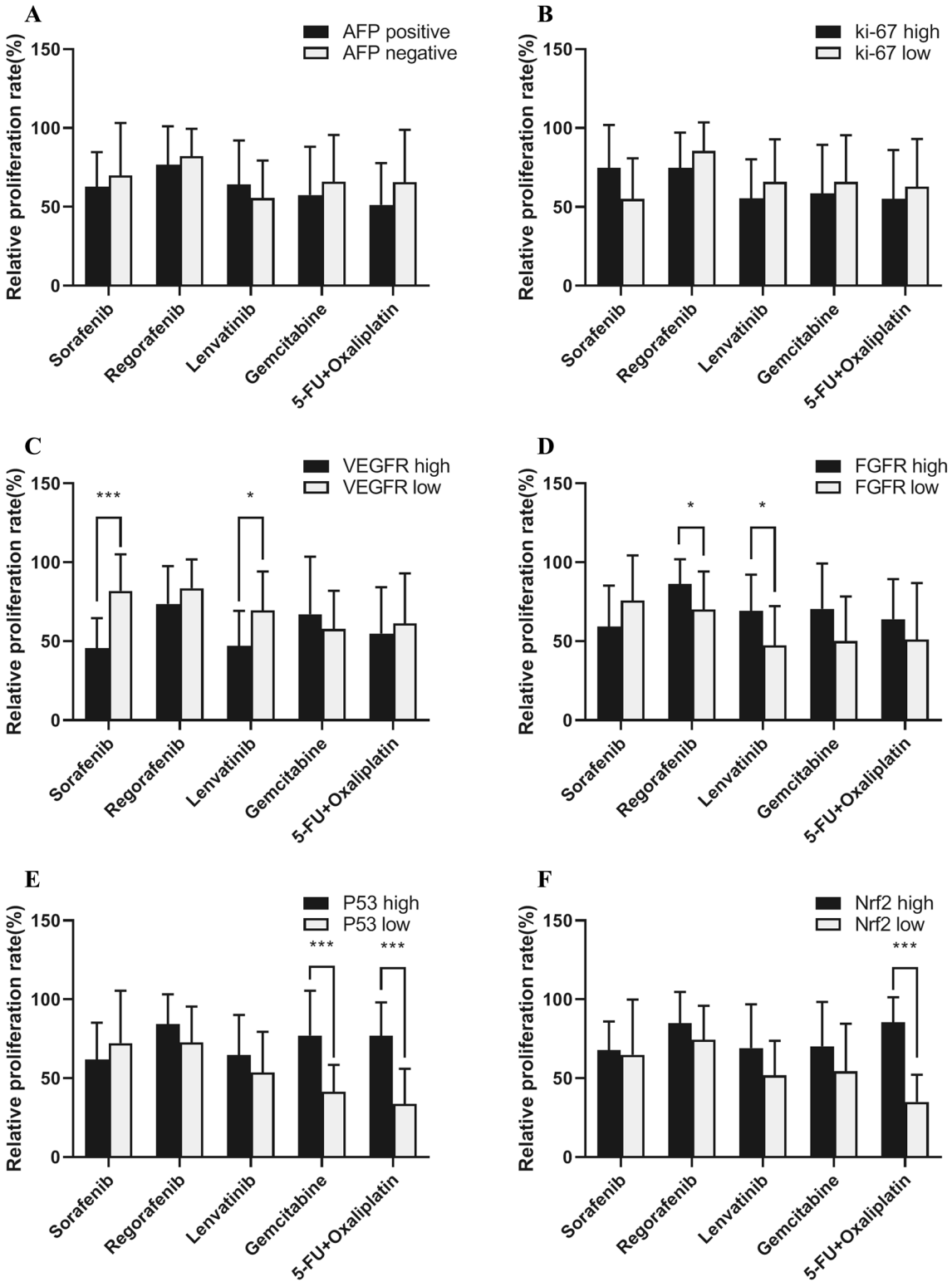

Fig. 5 Correlation between drug sensitivity and biomarkers. The relationship between the efficacy of the five drugs (Regorafenib, Regorafenib, Lenvatinib, Gemcitabine, and 5-FU + Oxaliplatin) and AFP (**a**), Ki-67 (**b**), VEGFR (**c**),FGFR (**d**), P53 (**e**), and Nrf2 (**f**) expression in patients with HCC. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; *t* test (two-tailed)

Sorafenib inhibits tumor cell proliferation by inhibiting the RAS/RAF/MEK/ERK signaling pathway, and blocks tumor neovascularization by inhibiting the activities of the glycine kinase receptor of vascular endothelial growth factor (VEGF-2) and platelet-derived growth factor (PDGF). Multicenter randomized controlled studies have confirmed that sorafenib could prolong the survival of patients with advanced HCC [11, 12]. In recent years, targeted drugs for HCC have continued to emerge. For example, envatinib was approved for the first-line treatment of unresectable HCC and regorafenib was approved for the second-line treatment after sorafenib treatment. Multiple centers have attempted to give different targeted drug treatment options after surgery to extend the tumor-free survival of patients to varying degrees.

With the advent of increasing number of targeted drugs and new chemotherapeutics, how to choose individualized drugs for patients has become a problem for clinicians. The PDX model could conserve the tumor microenvironment of the primary tumor. Compared to the previous CDX, it has the pathophysiological characteristics, histology and phenotypic characteristics of the primary tumor. The drug sensitivity test based on it has higher consistency with clinical application, which is crucial in accurate tumor treatment [13, 14]. However, the long modeling period and low tumor take rate of the PDX model restrict its clinical application. For HCC, we performed PDX modeling on the tumor tissues of the HCC patients enrolled in the same period and found that the tumor formation cycle takes about 6–10 months, and the tumor formation rate is only 32.1% (9/28). MiniPDX drug sensitivity test is a fast and effective alternative to the PDX model, which can obtain the primary tumor tissue response to the drug. This model can simulate the patient's clinical response to the drug and has a high sensitivity and specificity [11]. At present, MiniPDX has achieved satisfactory clinical application in the treatment of gallbladder cancer and duodenal adenocarcinoma [12, 15]. The screening of chemotherapeutic drugs and targeted drugs using this model in this study can be completed within 2 weeks after operation, and the success rate of screening drugs is high, which can better meet the clinical needs of patients.

The molecular biological characteristics of HCC include epidermal growth factor (EGFR) overexpression, excessive activation of cell division signaling pathways (such as the RAF/MAPK/ERK pathway), and abnormal vascular proliferation. Molecular targeted drugs developed for these molecular biological properties include EGFR receptor inhibitors (gefitinib, erlotinib, cetuximab), VEGF receptor inhibitors (bevacizumab), endothelial cells proliferation inhibitors (thalidomide), multi-target kinase inhibitors (sorafenib, sunitinib, lenvatinib, apatinib), etc. At present, the drugs widely used in clinical practice and approved by the FDA for treating HCC are mainly multi-target kinase inhibitors such as sorafenib, lenvatinib, and regorafenib. Several clinical studies have confirmed that these targeted drugs can effectively prolong the survival of patients with advanced HCC [16–18]. In addition, compared with other solid cancers, HCC is considered to be a chemotherapy-resistant tumor, which is related to its overexpression of dihydropyrimidine dehydrogenase, P-glycoprotein gene product and multidrug resistance gene MDR-1; hence, systemic chemotherapy is only used to treat HCC that cannot be surgically removed or is given by transcatheter arterial chemoembolization [19, 20]. In previous studies, almost all chemotherapeutics have been used to try to treat HCC, but only fluorouracil, platinum and gemcitabine have been proven effective for advanced HCC. Only FOLFOX4 (5Fu + Oxaliplatin) has passed the certification of large-scale phase III clinical research [21]. Therefore in this study, we chose five options: sorafenib, lenvatinib, regorafenib, gemcitabine, and 5Fu + oxaliplatin.

According to the previous reports, we believe that the drug can effectively inhibit tumor growth when the relative proliferation rate detected by MiniPDX is less than 55%. We then found that the average effective rates of sorafenib, regorafenib, lenvatinib, gemcitabine, 5Fu + oxaliplatin were 32.14, 10.71, 39.29, 50.00, and 46.43%, respectively. Among them, the effectiveness of screening cytotoxic drugs is slightly higher than that of targeted drugs. There may be two reasons: (1) The tumor cells in MiniPDX did not form a tissue block, and there was no corresponding tumor stroma and neovascularization. An important anti-tumor effect of targeted drugs is anti-angiogenesis; (2) MiniPDX has a shorter observation period (only 1 week), and targeted drugs have a slower effect than cytotoxic drugs. Therefore, we believed that the sensitivity of screening for targeted drugs by MiniPDX is lower than that of cytotoxic drugs. Nevertheless, the experimental group in this study achieved satisfactory clinical treatment results. Using the MiniPDX model to screen anti-tumor drugs for prophylactic treatment after operation, the overall survival rate and tumor-free survival rate of patients can be significantly prolonged. Because the targeted drugs we choose are multi-target kinase inhibitors, for example, sorafenib, they can act on Raf kinase to inhibit cancer cell proliferation [22]. Both lenvatinib and regorafenib are multi-target tyrosine kinase inhibitors, which can also directly inhibit the proliferation of cancer cells. Therefore, the MiniPDX model can also simulate the efficacy of this multi-target kinase inhibitor to a certain extent.

By analyzing the relationship between the drug sensitivity results and the patient's biomarkers, we found that sorafenib and lenvatinib are more sensitive to patients with a high expression of VEGFR. The anti-tumor effect of lenvatinib and regorafenib on patients with high FGFR expression is more obvious, which is consistent with their target of action. We also found that the efficacy of two groups of cytotoxic drugs in patients with high p53 expression was poor, and

5Fu + oxaliplatin was less sensitive to tumors with high Nrf2 expression, suggesting that the high expression of Nrf2 was related to platinum drug resistance [23]. Although some studies suggested that AFP and Ki-67 may cause hepatocellular carcinoma to develop resistance to certain chemotherapeutic drugs [24], no corresponding results were observed in this study.

Conclusions

Our clinical research confirm that MiniPDX is a fast and effective screening model for anti-tumor drugs. It has certain guiding significance for the selection of preventive medicine after partial liver resection for HCC and can improve the long-term survival of patients. Because there is no tumor angiogenesis in the model, this method is less sensitive to targeted drugs than to chemotherapy drugs. In the future, new and more efficient and comprehensive drug sieve models need to be developed to help clinicians use drugs rationally. In addition, some patients in this study screened two or more effective drugs through the MiniPDX model, but because the drugs are preventive medications, we have not selected a combination treatment mode; hence, we cannot evaluate the combination of two or more effective drugs. More tumor indications should be expanded in future studies.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interests.

References

1. Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA: Cancer J Clin 68(6):394–424
2. Kulik L, El-Serag HB (2019) Epidemiology and management of hepatocellular carcinoma [J]. Gastroenterology 156(2):477-491 e471
3. Hernandez MC, Bergquist JR, Leiting JL et al (2019) Patient-derived xenografts can be reliably generated from patient clinical biopsy specimens [J]. J Gastrointest Surg: Off J Soc Surg Aliment Tract 23(4):818–824
4. Malaney P, Nicosia SV, Dave V (2014) One mouse, one patient paradigm: new avatars of personalized cancer therapy [J]. Cancer Lett 344(1):1–12
5. Tentler JJ, Tan AC, Weekes CD et al (2012) Patient-derived tumour xenografts as models for oncology drug development [J]. Nat Rev Clin Oncol 9(6):338–350
6. Huynh H, Ong R, Soo KC (2012) Foretinib demonstrates antitumor activity and improves overall survival in preclinical models of hepatocellular carcinoma [J]. Angiogenesis 15(1):59–70
7. Zhang F, Wang W, Long Y et al (2018) Characterization of drug responses of mini patient-derived xenografts in mice for predicting cancer patient clinical therapeutic response [J]. Cancer Commun 38(1):60
8. Zhan M, Yang RM, Wang H et al (2018) Guided chemotherapy based on patient-derived mini-xenograft models improves survival of gallbladder carcinoma patients [J]. Cancer Commun 38(1):48
9. Cwinn M, Molinari M (2016) Regional variations in treatment modalities for hepatocellular carcinoma in Canada [J]. Hpb 18:e196–e197
10. Raza A, Sood GK (2014) Hepatocellular carcinoma review: current treatment, and evidence-based medicine [J]. World J Gastroenterol 20(15):4115–4127
11. Llovet JM, Bruix J (2008) Molecular targeted therapies in hepatocellular carcinoma [J]. Hepatology 48(4):1312–1327
12. Rimassa L, Santoro A (2009) Sorafenib therapy in advanced hepatocellular carcinoma: the sharp trial [J]. Expert Rev Anticancer Ther 9(6):739–745
13. Khandelwal G, Girotti MR, Smowton C et al (2017) Next-generation sequencing analysis and algorithms for pdx and cdx models [J]. Mol Cancer Res: MCR 15(8):1012–1016
14. Koga Y, Ochiai A (2019) Systematic review of patient-derived xenograft models for preclinical studies of anti-cancer drugs in solid tumors [J]. Cells 8(5):418
15. Zhao P, Chen H, Wen D et al (2018) Personalized treatment based on mini patient-derived xenografts and wes/rna sequencing in a patient with metastatic duodenal adenocarcinoma [J]. Cancer Commun 38(1):54
16. Cheng A-L, Finn RS, Qin S et al (2017) Phase iii trial of lenvatinib (len) vs sorafenib (sor) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uhcc) [J]. J Clin Oncol 35(15_suppl):4001–4001
17. Llovet J, Cheng A, Qin S et al (2019) 6519 efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma (hcc): collective results from the phase III sorafenib HCC assessment randomized protocol (sharp) and Asia-Pacific (AP) trials [J]. Eur J Cancer Suppl 7(2):367
18. Llovet JM (2008) Sorafenib in advanced hepatocellular carcinoma [J]. N Engl J Med 359(23):2498 **(author reply 2498–2499)**
19. Ikeda M, Mitsunaga S, Ohno I et al (2015) Systemic chemotherapy for advanced hepatocellular carcinoma: Past, present, and future [J]. Diseases 3(4):360–381
20. Kudo M, Trevisani F, Abou-Alfa GK et al (2016) Hepatocellular carcinoma: therapeutic guidelines and medical treatment [J]. Liver cancer 6(1):16–26
21. Qin S, Cheng Y, Liang J et al (2014) Efficacy and safety of the folfox4 regimen versus doxorubicin in Chinese patients with advanced hepatocellular carcinoma: a subgroup analysis of the each study [J]. Oncologist 19(11):1169–1178
22. Ikeda M, Morizane C, Ueno M et al (2018) Chemotherapy for hepatocellular carcinoma: current status and future perspectives [J]. Jpn J Clin Oncol 48(2):103–114

23. Raghunath A, Sundarraj K, Arfuso F et al (2018) Dysregulation of nrf2 in hepatocellular carcinoma: role in cancer progression and chemoresistance [J]. Cancers 10(12):481
24. He C, Li L, Guan X et al (2017) Mutant p53 gain of function and chemoresistance: the role of mutant p53 in response to clinical chemotherapy [J]. Chemotherapy 62(1):43–53