Drug effect analysis of sorafenib combined with transcatheter arterial chemoembolization in the treatment of advanced hepatocellular carcinoma

Xiangsu Xu[1] and Qingshun Meng[2]*
[1]Department of Hepatobiliary Surgery, Jining No.1 People's Hospital, 6 Health Street, Jining, Shandong, China
[2]Department of Gastroenterology, Jining No.1 People's Hospital, 6 Health Street, Jining, Shandong, China

Abstract: Sorafenib is a new multi-target oral drug that inhibits many kinds of protein kinase small molecules to treat tumors. Currently, sorafenib is one of the drugs that permit systemic treatment of liver cancer in the middle stage. Although sorafenib has good therapeutic effect on liver cancer, the clinical effect of sorafenib alone in the treatment of liver cancer is limited. This study compared the efficacy of sorafenib, TACE (transcatheter arterial chemoembolization), and sorafenib combined with TACE in the treatment of liver cancer patients. The results showed that the curative effect of sorafenib combined with transcatheter arterial chemoembolization is better than that of hepatic artery chemoembolization or sorafenib orally. The total effective rate of combined treatment is 93.8%, while the effective rate of arterial chemoembolization and sorafenib is 64.1% and 72.2% respectively. Combined treatment can significantly prolong the total survival of the patients with liver cancer, which is significantly different from that of arterial chemoembolization or sorafenib alone.

Keywords: Sorafenib, transcatheter arterial chemoembolization, drug effect, tumor cell.

INTRODUCTION

HCC (Hepatocellular carcinoma) is the most common primary malignant tumor of the liver (Balmadrid *et al.*, 2015; Cho *et al.*, 2012). Among the world's most common cancers, liver cell cancer ranks at the fifth place, ranking third among the most common causes of cancer related deaths (Emir *et al.*, 2014). In Europe and the United States, it is the leading cause of death in patients with cirrhosis, China alone occupies 55% of the world's cases (Espinel *et al.*, 2015, Hou *et al.*, 2015). The incidence of male liver cancer is higher than that of women, with a total sex ratio of about 2.4 (Gunaldi *et al.*, 2015). The early symptoms of HCC are occult and the patients are mostly in the middle and late stages. Internationally, a more mature and authoritative BCLC (Barcelona clinic liver cancer) staging system is the latest HCC treatment guideline (Han *et al.*, 2015). Only 30% of the patients who had early radical treatment included surgical resection, liver transplantation and PEI (percutaneous ethanol injection)/RF (efficacy of radiofrequency). The 5 year survival rate was 50% to 70% (Lim *et al.*, 2012).The median and late stage patients account for about 50% of the total number of patients (Koh *et al.*, 2013, Jia *et al.*,2015, Manzat *et al.*, 2015). The 3-year survival rate of TACE and sorafenib alone is 10% to 40%, and the 20% of the end stage patients can only be symptomatic treatment, their survival time is less than 3 months (Huang *et al.*, 2015, Kertmen *et al.*, 2015).

Compared to systemic chemotherapy, the advantage of hepatic arterial chemoembolization (TACE) is to deliver high concentration of drugs to the tumor site and reduce systemic exposure (Hou *et al.*, 2015, Kim, 2016). It is reported that arterial embolization can make the patients with 15%-55% partially remission and significantly delay the progression of the tumor and the invasion of the blood vessels (Liu *et al.*, 2017, Tim *et al.*, 2017). A systematic review of a randomized clinical trial of non resectable hepatocellular carcinoma and meta-analysis showed that chemoembolization could prolong the survival of the patients (Mukai *et al.*, 2012, Pengfei *et al.*, 2016). People who are best suited for chemoembolization are patients with good liver function and asymptomatic multiple nodular tumors, with no vascular invasion or extrahepatic diffusion (Pan *et al.*, 2014). However, TACE treatment usually does not make the lesion completely necrotic, and the long-term survival rate is still not ideal (Miyahara *et al.*, 2012, Li *et al.*, 2015). It has been confirmed that there are various angiogenesis factors in tumor patients, the vascular endothelial growth factor VEGF(vascular endothelial growth factor) is the strongest angiogenesis factor in vivo (Nishida *et al.*, 2015, Jordi *et al.*, 2017). Studies have shown that the protein expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (B FGF) in the TACE treatment group is significantly higher than that in the non TACE treatment group, and there is a significant difference between the two groups (Okada *et al.*, 2011, Sanomura *et al.*,2014). TACE induced hypoxia and hypoxia can increase VEGF expression and stimulate growth of liver tumor cells, leading to residual tumor progression, metastasis and even new tumor formation. If we can inhibit angiogenesis on the basis of TACE, it may

**Corresponding author:* e-mail: mengqingshun0609@163.com

significantly improve the survival time of HCC patients, reduce metastasis and recurrence (Shi *et al.,* 2015, Tian *et al.,* 2015).

Recently, the research results have shown that the tumor molecular targeted therapy has a good safety and effectiveness, especially for the multi-target Raf kinase inhibitor, drug epidermal growth factor receptor and vascular endothelial growth factor target, has achieved good effect in clinical practice (Takeuchi *et al.,* 2013; Ostojic *et al.,* 2015). Sorafenib is a kind of multi kinase inhibitor, which can play a role in tumor proliferation and angiogenesis. Although sorafenib has good therapeutic effect on liver cancer, the clinical effect of sorafenib alone in the treatment of liver cancer is limited.This study compared the efficacy of sorafenib, TACE and sorafenib combined with TACE in the treatment of patients with liver cancer, and observed the difference between the adverse reactions and the overall survival time.

MATERIALS AND METHODS

156 patients with liver cancer treated in our hospital in 2016 were examined by histopathology, ultrasound, CT, and magnetic resonance (MRI).Exclusion criteria: those who had received other antitumor drugs or had undergone hepatic arterial infusion chemotherapy. The history of heart disease, congestive heart failure NYHA Level 2 or above, symptomatic coronary artery disease or require treatment with drugs or β blockers of digoxin arrhythmia; human immunodeficiency virus (HIV) infection; severe active clinical infection, HBV and HCV infection except; not oral drugs; recently accepted surgical treatment of large. General information is shown in table 1. All patients were approved by Ethics Committee of our hospital and signed on the informed consent.

TACE

53 patients with liver cancer were randomly selected to receive TACE treatment. In the DSA perspective, the 5-Fr catheter was inserted into the femoral artery and the tip of the catheter was inserted into the blood supply branch of the tumor. Identification of tumor target artery, according to liver function and tumor size, injection of 2~20 ml cisplatin with lipiodol emulsion prepared according to the proportion of 1:1.

Sorafenib treatment

54 patients were given sorafenib 400 mg orally, 2 times 1 day, and 12 weeks were continuously treated. The other 49 patients began to take sorafenib orally at the interval of TACE treatment, with the same use.

STATISTICAL ANALYSIS

SPSS 19 software was used for statistical analysis. The survival analysis was carried out by Kaplan-Meier method. The count data were tested by x2, and the difference of $P<0.05$ was statistically significant.

RESULTS

Clinical baseline characteristics

The basic clinical features of all the patients before treatment were shown in table 1. After treatment, 12 week, the curative effect of each group was shown in table 2. The dual action mechanism of sorafenib (tumor cell proliferation inhibition and angiogenesis inhibition) combined with the proven effect of the drug on advanced hepatocellular carcinoma. As can be seen from table 1, the combined treatment group consisted of 49 cases, 33 men and 16 women, of which 38 cases were 0-1 in ECOG method, 11 in the rest, HBV in 41, and 7 with HVCV. The arterial chemoembolization group consisted of 53 cases, of which 39 were male and 14 women, including 45 cases of ECOG physical status score 0-1, the remaining 8, 49 patients with HBV, and 12 with HVCV. Group sorafenib consisted of 54 cases, including 45 males and 9 females, of which 43 cases were ECOG's physical condition score 0-1, the remaining 11 cases, 45 cases had HBV, 7 cases had HVCV. There was no significant difference in clinical characteristics between the patients in each group.

Treatment effect

As can be seen from table 2, in the combined treatment group, 3 cases were completely effective, 11 cases were partially effective, 32 cases were stable, 3 cases were invalid, and the total effective rate was 93.8%. In the arterial chemoembolization group, 1 cases were completely effective, 12 cases were partially effective, 21 cases were stable, 19 cases were ineffective, and the total effective rate was 64.1%. In Sorafenib group, 0 cases were completely effective, 12 cases were partially effective, 27 cases were stable, 15 cases were ineffective, and the total effective rate was 72.2%. The effect of combined treatment group was significantly stronger than that of the other two groups, and the results were statistically different ($P<0.05$).

DISCUSSION

Liver cancer is one of the most common cancers. Some patients with liver cancer often have other tumors or diseases, which make them unable to endure or are no longer suitable for systemic treatment (Mannen *et al.,* 2010). This type of liver cancer is no longer suitable for surgical treatment, and TACE or oral targeting anticancer drugs may have a certain therapeutic effect on this type of liver cancer. The study shows that the patients with liver cancer choose the appropriate treatment methods without the influence of age and other factors, and have the ideal effect of clinical treatment (Sheng *et al.,* 2015). Transcatheter arterial chemoembolization (TACE) is an interventional therapy for liver cancer patients who cannot tolerate surgical excision. However, many people

Table 1: General information

Project	n	Percentage (%)
Gender		
Male	94	60.2
Female	62	39.8
Hepatitis		
Hepatitis B	130	83.3
HCV	17	10.8
No	9	5.8
Clinical stage of Barcelona Clinic Liver Cancer		
Stage B	87	55.7
Stage C	69	44.3

Table 2: Clinical baseline characteristics

Classification	Combined treatment (n=49)	Arterial chemoembolization (53)	Sorafenib (54)
Gender			
Male	33	39	45
Female	16	14	9
Age (age)			
<50	27	22	25
≥50	22	32	29
ECOG method of physical status score			
0-1	38	45	43
2	11	8	11
Pathogeny			
HBV	41	39	45
HCV	7	12	7
Other	1	2	2
Classification of liver function			
A level	28	27	35
B level	21	26	19
Distant organ transfer	31	32	30
Serum AFP≥400 ng/m L	28	37	26

Table 3: treatment effect

Effect	Combined treatment (n=49)	Arterial chemoembolization (53)	Sorafenib (54)
Fully effective	3	1	0
Partial validity	11	12	12
Stability of the disease	32	21	27
Invalid	3	19	15
Total effective rate	93.8%	64.1%	72.2%

believe that age is a major factor in limiting TACE. Recent studies have reported that the combination of appropriate therapeutic drugs and TACE in the treatment of liver cancer is better (Suzuki *et al.,* 2014). More and more studies have shown that TACE can effectively control the infiltration of blood vessels and tumor metastasis in patients with liver cancer (Takizawa *et al.,* 2008, Yoshio *et al.,* 2013).

Sorafenib is a new and multi-target oral drug for the treatment of tumor with small molecules that inhibit many protein kinases. At present, sorafenib is one of the drugs that permit systemic treatment of liver cancer in the middle stage (Wojtukiewicz *et al.,* 2015, Gunaldi *et al.,* 2015). It is suitable for sorafenib patients with vascular invasion, extrahepatic metastasis or poor response to transcatheter arterial chemoembolization. Studies show that sorafenib is the main drug to prolong the progression and survival of patients with liver cancer (Emir *et al.,* 2014, Xiao *et al.,* 2015). The results of the third phase

clinical trial show that sorafenib can significantly prolong the time of disease progression and improve the survival time of patients, and has a good therapeutic effect on patients with liver cancer (Han *et al.,* 2015). Even with the continuous development of drugs and interventional techniques, a single treatment cannot meet the clinical efficacy of this uncontrollable disease (Balmadrid *et al.*, 2015, Cho *et al.,* 2012). Therefore, the study of new clinical treatment plans is imminent. The combination of sorafenib and TACE has shown unique advantages in the clinical treatment of liver cancer.

CONCLUSION

The results showed that sorafenib combined with transcatheter arterial chemoembolization and the curative effect is better than that of TACE or sorafenib orally, combined treatment can significantly prolong overall survival in patients with hepatocellular carcinoma, and arterial chemoembolization or sorafenib therapy alone compared with significant difference. Sorafenib combined with transcatheter arterial chemoembolization is effective and safe for patients with liver cancer. It has good clinical effects in delaying the progression of tumor and prolonging the survival time of patients with liver cancer. Further randomized controlled trials are needed to confirm the therapeutic effect of sorafenib combined with hepatic artery chemoembolization on patients with advanced liver cancer.

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