Full Length Research Paper

Efficacy of Transcatheter Arterial Chemoembolization (TACE) combined with sorafenib in the treatment of advanced hepatocellular carcinoma

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This study investigated the efficacy and toxic effects of the combination of transcatheter arterial chemoembolization (TACE) with sorafenib in patients with advanced hepatocellular carcinoma (HCC). Thirty-five cases clinically diagnosed as having HCC were enrolled in the study from January, 2009 to December, 2010. All the patients received TACE combined with sorafenib (400 mg) twice per day. The tumour response was evaluated according to the modified Response Evaluation Criteria in Solid Tumours (mRECIST) criteria following every 4 to 6 weeks. Moreover, safety and response were assessed. TACE in combination with sorafenib was successfully administered in 33 patients: mean age, 52.6 years; child's A, 76%; Barcelona Clinic Liver Cancer (BCLC) stage C, 46%; and Eastern Cooperative Oncology Group performance status of 0, 1 and 2, 27%, 64% and 9% respectively. Among the 33 cases that were evaluated, complete response was achieved in 2 cases, partial response in 14 cases, stable disease in 11 cases, and stable progressive disease in 6 cases. The total disease control rate was 81.8%, median time to tumour progression was 8.6 months, and time was 15.4 months. The most common toxicities were hand-foot skin reaction (63.6%), fatigue (60.6), and anorexia (54.5%). The combination of sorafenib and TACE in patients with unresectable HCC resulted in longer survival time. In addition, the treatment was well tolerated and safe.

Key words: Combined transcatheter arterial chemoembolization (TACE), sorafenib, hepatocellular carcinoma (HCC).

INTRODUCTION

Hepatocellular carcinoma (HCC) is currently the fifth most common solid tumour worldwide and the third major cause of cancer-related death (Verslype et al., 2009). Few effective treatment options are available for HCC patients (Llove et al., 2008; Cheng et al., 2009). Only about 15% of patients have the opportunity for surgical resection; most of the patients can only carry on the comprehensive therapy by transcatheter arterial chemoembolization (TACE) (Llovet et al., 2008). No standard systemic therapy was available before the advent of sorafenib, especially for patients diagnosed at an advanced stage or with progression after loco-regional therapy (Llove et al., 2008; Cheng et al., 2009). Systemic pharmacotherapy is usually the final and main treatment for advanced-stage disease. Conventional chemotherapy and surgical adjuvants are ineffective for patients with advanced HCC. However, it is often difficult to achieve complete necrosis of the tumour lesions with TACE treatment, and the newly formed tumour blood vessels of the collateral blood supply continue to grow once again. Maximising block tumour angiogenesis at the same time may allow TACE to significantly improve the clinical therapeutic effect in HCC patients, as shown in the Study of Heart and Renal Protection (SHARP) trial, the first successful molecular targeted therapy for HCC treatment (Llove et al., 2008). Sorafenib is an oral multi-target, multi-kinase inhibitor, which can not only inhibit tumour cell growth, differentiation, and proliferation, but also play

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a role in human angiogenesis system and inhibition of tumour angiogenesis (Abou-Alfa et al., 2006; Abou-Alfa 2009). The safety, tolerance, and effectiveness of combining sorafenib with TACE remain unknown, with no prospective clinical data currently available. In the present study, TACE combined with sorafenib was applied in HCC in the hope of receiving better clinical outcomes.

PATIENTS AND METHODS

Study population and eligibility

Patients with a diagnosis of unresectable HCC based on histologic examination from January, 2008 to December, 2010 were included. The eligibility criteria were as follows: Child–Pugh liver function of A/B; Eastern Cooperative Oncology Group performance status of 0 to 2; total bilirubin ≤3 mg/L; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than five times the upper limit of normal; prothrombin activity time less than 6 s; creatinine levels less than one point, five times the upper limit of normal; absolute neutrophil count ≥1500 μl\(^{-1}\); and haemoglobin ≥90 g/L. At least one target lesion can be detected according to the modified Response Evaluation Criteria in Solid Tumours (mRECIST) (Therasse et al., 2000). Thirty-three cases of drug use of more than 12 weeks were brought into the clinical observation data. Table 1 shows the specific clinical data.

Barcelona Clinic Liver Cancer (BCLC) classification was used to categorize the stage of cancer (Llovet and Bruix, 2008). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee, the Second Affiliated Hospital of Nanchang University. Written informed consent was obtained from all participants.

Study design

The patients were treated by TACE. A 5-F RH catheter was inserted into the hepatic artery by Seldinger technique, and the blood supply to the lesion was cleared using a conventional angiography. The target vessels were embolised with mitomycin C, doxorubicin, or epirubicin, oxaliplatin plus iodatol emulsion or with gelatin sponge particles or microspheres that enhances lesions. The total dose delivered was determined by the size of the lesion(s) to be treated. Sorafenib dose reductions (that is, 400 mg once daily, 400 mg every other day) and drug interruptions were allowed for toxicities. The decision whether to repeat the TACE treatment depended on the tumour embolism and iodatol deposition conditions.

Study endpoints

The endpoints were efficacy and toxic effects associated with TACE combined with sorafenib in patients with unresectable HCC. The patients who received one or more doses of sorafenib were included in the evaluation and assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were calculated using the mRECIST criteria. The time was 4 to 6 weeks after treatment. The disease control rates were equal to CR plus PR plus SD. Time to tumour progression (TTP) is defined as the time from the beginning to tumour progression. Overall survival (OS) was from the start of treatment to the date of death or the last follow-up.

Statistical analysis

The statistical package for social sciences (SPSS) 17.0 software was used for statistical analysis. Kaplan–Meier method was used for survival analysis.

RESULTS

Safety and treatment toxicity

All the 33 patients except 2 that enrolled in the study were treated with sorafenib therapy. The most common
toxicities were as follows: hand-foot skin reaction (HFSR; 64%), emaciation (61%), fatigue (55%), rash (33%), diarrhoea (33%), alopecia (24%), abdominal pain (18%), gingival bleeding (18%), hypertension (3%), and uncommon toxicities (grades 3 to 4) such as hypertension, HFSR (18%), rash (6%), and fatigue (3%). All patients were able to continue after clinical management of adverse reactions; the symptoms were relieved a month later. Table 2 shows the incidence of adverse reactions.

### Efficacy and survival analysis

Thirty-three patients were evaluated for treatment response. Follow-up time ranged from 4.6 to 30.0 months (median follow-up time of 11.0 months). Thirteen patients died at the end of the follow-up, 2 patients achieved CR, 14 patients achieved PR, 11 patients achieved SD, and 6 patients achieved PD (Table 3). The disease control rate was 81.8%, median time to tumour progression was 8.6 months, and median overall survival time was 15.4 months (Figure 1).

### DISCUSSION

TACE is a modality frequently utilized. Recent data have suggested that TACE may be a better loco-regional approach because it may allow better drug delivery, reduced systemic drug exposure, and decreased adverse effects (Hong et al., 2006; Lammer et al., 2010).

In accordance with Pawlik et al. (2011), our study showed that disease control was attained at 81.8% by RECIST criteria (Therasse et al., 2000). Pawlik et al. (2011) reported that 11 used a combination of drug-eluting beads-transarterial chemoembolization (DEB-TACE) and sorafenib in 35 patients with advanced unresectable hepatocellular carcinoma, of whom 64% were BCLC stage C that were treated with systemic therapy (Llovet et al., 1999). Moreover, a median number of two DEB-TACE cycles (range, 1 to 5 cycles) was found. Seventeen percent of all reported toxicities were of grades 3 and 4, which is modest in this patient population. The study by Pawlik et al. (2011) not only confirmed the necessity of the multidisciplinary approach to treating HCC, but also identified the importance of tumour biology by attempting to make up for the increase in angiogenesis induced by embolization (Sergio et al., 2008; Wang et al., 2008). Moreover, the use of an antiangiogenic therapy in combination with transarterial embolization (TAE) is supported in a preclinical model to cause a reduction in tumour volume and vessel density, also a prolongation of survival compared with only TAE (Jiang et al., 2007).

The most common toxicities such as fatigue, dermatologic adverse effects (HFSR and rash), and right upper quadrant pain were similar to other studies (Hsu et al., 2010a; Cheng et al., 2012). This toxicity profile was also similar to those reported in the SHARP (Llovet et al., 2008) and Asia-Pacific (Cheng et al., 2009) trials, which noted diarrhoea, HFSR, anorexia, and alopecia as the more common toxicities. Treatment-related adverse events (AEs) of any grade in our data were HFSR (63.6%), emaciation (61%), fatigue (55%), diarrhoea (33%), rash (51%), alopecia (24%), abdominal pain (18%), gingival bleeding (18%), and hypertension (3%). The incidence of treatment-related AEs of any grade was 34%. Long-term administration of sorafenib will lead to a higher cumulative incidence of AEs. The most frequently reported AEs were HFSR, fatigue, diarrhoea, rash, and alopecia. The results suggest that therapy beyond disease progression may be feasible for some patients if there is a clinical benefit prior to reaching the progression-free survival (PFS) time point. The results demonstrate that sorafenib is well tolerated during long-term administration. AEs presented early in the course of treatment, and did not mean future intolerance to sorafenib. On the contrary, treatment through toxicity may allow patients to achieve tumour control with sorafenib.

Different from the traditional adverse effects from chemotherapeutic agents, sorafenib may have a distinct adverse effect profile. Sorafenib has been shown to increase the risk of bleeding, HFSR, hypertension, and arterial thromboembolism (Wu et al., 2008; Hsu, 2009; Choueiri et al., 2010). Although, 33 of 35 patients treated with combined sorafenib and intra-arterial doxo-rubicin had grades 3 to 4 toxicity, these toxicities were
manageable. The toxicity profile of sorafenib plus TACE was similar to that of sorafenib alone, with anorexia, fatigue, and dermatologic adverse effects among the most common. TACE- and sorafenib-related toxicities are difficult to discern, yet the toxicity profile for sorafenib plus TACE was similar to those noted in the SHARP and Asia-Pacific sorafenib-only trials. Given that most of the patients’ HFSR appears to respond well to sorafenib, the emergence of HFSR may be associated with efficacy (Strumberg et al., 2006). However, the Child–Pugh classification is confirmed to be closely related to the efficacy of sorafenib (Llovet et al., 2008; Pinter et al., 2009). In addition, the timing may be considerable as shown in the TACE and sorafenib study reported by Kudo et al. (2011). The different results may be due to the timing of antiangiogenic therapy with sorafenib (Pawlik et al., 2011). The optimal clinical treatment will depend on the balance between safety and efficacy. The series of dosing added to the period as reported by Pawlik et al. (2011) comes at a time when those concepts are better defined. However, the descriptions of this technique remain nonspecific, and the major features in the validation of the criteria have not been confirmed.

The objectives of this study were to investigate the efficacy and toxic effects of sorafenib combined with TACE in advanced HCC patients. Data from this study strongly suggest that sorafenib combined with TACE is a safe and relatively well-tolerated therapy. However, the chronic nature of relapsed HCC shows an important implication of therapeutic regime for both oncologists and patients. Treatment optimization depends on the cancer behaviour in the individual patient and benefits from proper therapy.

In addition, to improve treatment efficacy for such complicated disease, the combined therapy with sorafenib and TACE or cytotoxic agents is being tested in several clinical trials. Antiangiogenic therapy represents one of the most significant milestones in the field of molecular targeted therapy for cancer treatment. The reason is that most advanced HCC patients in Asian countries, where chronic hepatitis B infection is the primary risk factor, usually have huge tumour burden and perhaps have been pretreated by loco-regional therapy such as ablation therapy and TACE (Cheng et al., 2009; Hsu et al., 2010a, b).

Conclusively, the combination of sorafenib and TACE in patients with unresectable HCC was well tolerated and safe. Data from the current study and other emerging trials should help determine whether the combination of sorafenib and TACE will become the standard of care for patients with unresectable HCC.

REFERENCES


