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A COMPARISON OF THE THERAPEUTIC EFFICACY OF TRANSARTERIAL CHEMOEMBOLIZATION AND COMBINATION THERAPY WITH TRANSARTERIAL CHEMOEMBOLIZATION PLUS SORAFENIB FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Abstract

[Background and Aims] The combination therapy of transarterial chemoembolization (TACE) plus sorafenib has been applied for unresectable hepatocellular carcinoma (HCC). However, its efficacy remains controversial, possibly due to the timing of the initiation of sorafenib treatment. We evaluated the efficacy of this combination therapy when sorafenib treatment was initiated soon after the patient recovered from the adverse events due to the initial TACE procedure. [Methods] This was a retrospective study at a single hospital. Twenty-three unresectable HCC cases who exceeded the up-to-seven criteria but who showed no major vascular invasion or extrahepatic metastasis were enrolled in this study. The patients were classified into two groups : Group C ($n=7$) received combination therapy ; Group T ($n=16$) received TACE as the sole therapy. The time-to-tumor progression (TTP) and overall survival (OS) of the two groups were compared. [Results] The median TTP in Groups C and T was 1,737 days and 422 days, respectively ($p < 0.05$). The median survival time (MST) after the initiation of each therapy in Groups C and T was 1,780 days and 371 days, respectively ($p < 0.05$). [Conclusion] The TTP and OS of patients with unresectable HCC who received TACE plus sorafenib (administered soon after the initial TACE procedure) were superior to those in patients who received TACE alone.

Key words : TACE, sorafenib, combination therapy, unresectable HCC

Introduction

Although unresectable hepatocellular carcinoma (HCC) is associated with a relatively poor prognosis, various therapeutic strategies have been developed to inhibit tumor growth and expansion and to extend the time of patients' survival. Transarterial chemoembolization (TACE) is widely utilized for these purposes and its efficacy is well established[1)]. However, during the repeated

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TACE therapy, HCC often becomes refractory to TACE and an alternative therapy is required.

Sorafenib, an inhibitor of multi-kinases including vascular endothelial growth factor (VEGF) and platelet-derived growth factor(PDGF) receptor tyrosine kinases[2], is currently used to treat advanced HCC and significantly improves the outcome, including overall survival[3,4]. Furthermore, it is reported to be effective in the treatment of TACE-refractory HCC[5].

Based on this knowledge, the combination therapy of TACE and sorafenib for unresectable HCC has been expected to improve its prognosis and various trials have been conducted and reported. Although several reports, including meta-analyses, have indicated that the combination therapy improved the time-to-tumor progression (TTP) of the patients with unresectable HCC[6,7], its efficacy with regard to the survival period remains controversial[6-8]. It is possible that this discrepancy with regard to the survival period is associated with the time lag between the initial TACE treatment and the administration of srafenib in each study[8]. Kudo *et al*., for example, noted that since > 50% of patients in their large scale study started sorafenib at > 9 weeks after TACE, TACE plus sorafenib did not prolong even the TTP[9]. Thus, we investigated the efficacy of this combination therapy in the treatment of the unresectable HCC with the administration of sorafenib started soon after the initial TACE procedure.

Subjects and Methods

Subjects

Twenty-five consecutive cases of unresectable HCC that exceeded the up-to-seven criteria (maximum tumor diameter [cm] + number of tumors ≤ 7)[10], but who showed no major vascular invasion or extrahepatic metastasis, were treated at Akita University Hospital between August 2009 and February 2016. The patients were classified into two groups, those who consented to the combination therapy and who were treated with the combination of TACE and sorafenib (n=9) ; and those who did not consent to the combination therapy and who were treated with TACE alone (n=16). The administration of sorafenib was discontinued prior to the second TACE procedure in two cases who were assigned to the combination therapy group (due to sorafenib-related adverse events). Thus, these 2 cases were excluded from this study. Consequently, the combination therapy group (Group C) and TACE alone group (Group T) included 7 patients and 16 patients, respectively. This study was approved by the ethics committee of Akita University. We obtained informed consent from all patients before their enrollment in this study. The study was conducted in accordance with the Declaration of Helsinki.

TACE procedure

A 4-Fr Catheter was inserted into the celiac artery through the femoral artery by Seldinger's method to perform angiography of the hepatic artery. After the angiography, a micro-catheter was inserted through the 4-Fr catheter selectively into the feeding arteries of the HCCs tumors. Then, the selected drug (epirubicin, cisplatin or miriplatin) was mixed with ethyl ester of iodinated poppy-seed oil fatty acid (Lipiodol®, Guerbet Japan, Tokyo, Japan) to form an emulsion. We infused the emulsion through the microcatheter. Finally, feeding arterial embolization was performed with gelatine sponge (Gelpart®, Nihon Kayaku, Tokyo, Japan or Spongel®, Asteras, Tokyo, Japan). Written informed consent was obtained from every patient before each TACE procedure.

The protocol of the combination therapy of sorafenib and TACE

Soon after the patients' recovered from the initial TACE-induced adverse events (*i.e.,* fever, liver enzyme elevation and/or appetite loss) sorafenib was administered at a dose of 400 mg or 800 mg. Consequently, the average of the time lag between the initial TACE procedure and the administration of srafenib in Group C was 22.3 days (range : 8-46 days). The second TACE procedure was scheduled for the 4th month after the first TACE procedure, and TACE was repeated on demand thereafter when viable lesion(s) were observed on computed tomography (CT) and/or magnetic resonance imaging (MRI). The administration of sorafenib was interrupted for 1 week before and after each TACE procedure. The dose of sorafenib was modified between 400 mg and 800

mg according to the presence (and severity), or absence of sorafenib-related adverse events, such as hand-foot-skin reactions and hypertension during the combination therapy. In Group T, TACE was carried out according to the same protocol as in Group C without the administration of sorafenib.

Statistical analysis

The continuous variables in Groups C and T were analyzed using the Mann-Whitney *U* test. The ratio of male to female of patients between the two groups was analyzed using Fisher's exact test. The TTP and overall survival (OS) were analyzed using Kaplan-Meier curves and the log-rank test. *P* values of < 0.05 were considered to indicate statistical significance.

Results

The characteristics of the patients in the TACE alone (Group T) and combination therapy with TACE plus sorafenib (Group C) groups

As shown in Table 1, the characteristics of the patients, including their age, gender, tumor size, Child-Pugh score, serum α-fetoprotein and PIVKA-II values were similar and no significant differences were observed between the two groups. In contrast, although the assignment of the cases into the two groups was solely dependent on the patients' consent with regard to the administration of sorafenib and was independent of factors associated with the disease progression including tumor size, tumor number and liver function, the number of tumors in C group was significantly greater than in group T (Table 1, $P < 0.01$).

TTP and MST

We next compared the TTP between the two groups the time for which the patient was refractory to TACE was defined as the endpoint[11]. A Kaplan-Meier curve analysis revealed that the median TTP in Group C and T was 1,737 days and 422 days, respectively (Figure 1). Furthermore, a log-rank test demonstrated that median TTP in Group C was significantly longer than that in group T (Figure 1, $p < 0.05$).

We next compared the median survival time (MST) of the two groups. A Kaplan-Meier curve analysis showed that the MST of Group C and T was 1,780 days and 371 days, respectively (Figure 2). A log-rank test revealed that MST in Group C was significantly longer than that in group T (Figure 2, $p < 0.05$).

The number of TACE procedures

Knowing that the TTP and MST were both significantly longer in Group C than in Group T, we compared the number of the TACE procedures between the two groups. As shown in Figure 3, the average number of TACE procedures in Groups C and T was 5.6 and 2.3, respectively. These data indicated that the patients in Group C underwent a significantly greater number of TACE procedures than those in Group T ($P < 0.01$, Figure 3).

Adverse events

We finally evaluated the adverse events in both groups. As shown in Table 2, sorafenib-related adverse events

Table 1. The characteristics of the patients in Groups T (TACE therapy) and C (combination therapy with TACE and sorafenib).

Characteristics	Group T	Group C	*P* value
Gender (Male/Female)	13/3	6/1	$P > 0.9$
Age	71±9	64±9	$P = 0.07$
Tumor size (cm)	5.8±2.2	4.9±2.3	$P = 0.28$
Number of tumors	3.1±2.1	7.6±2.5	$P < 0.01$
Serum α-fetoprotein (ng/ml)	5,130±10,827	429±1,057	$P = 0.54$
Serum PIVKA-II (IU/ml)	31,383±94,229	585±633	$P = 0.08$
Child-Pugh Score	5.8±0.9	5.1±0.4	$P = 0.10$

Unless otherwise indicated, the values indicate the ratio or the mean ± SD.

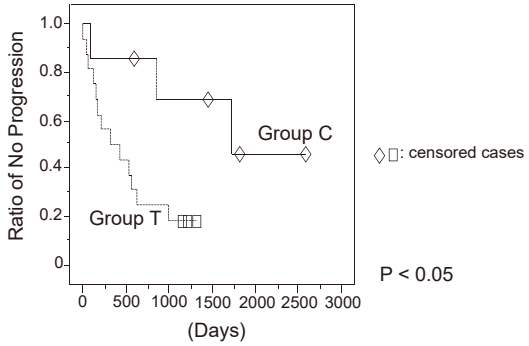

Figure 1. The estimation of the TTP of Groups C and T. The TTP was analyzed and compared by a Kaplan-Meier Curve analysis and the log-rank test.

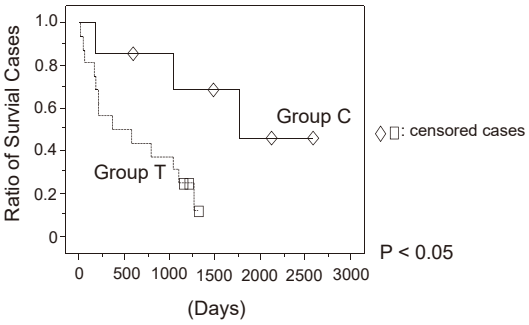

Figure 2. The estimation of survivals in Groups C and T. The MST was analyzed and compared by a Kaplan-Meier Curve analysis and the log-rank test.

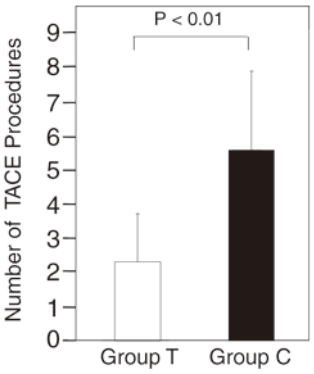

Figure 3. The number of TACE procedures in Groups C and T.

were observed in all of the patients who received combination therapy during the study period, including the patients who were excluded from the study. The adverse events included hand-foot-skin reaction, hypertension, anorexia and liver enzyme elevation. In all cases in Group C, the sorafenib-related adverse events were treated conservatively. The methods of conservative treatment included dose reduction without the discontinuation of sorafenib. In the two patients who were excluded from this study, the severe effects, which included liver enzyme elevation (AST and ALT became elevated to a maximum of 395 IU/L and 286 IU/L, respectively), anorexia and a hand-foot-skin reaction, improved soon after the cessation of sorafenib.

Discussion

We reported that the combination therapy of TACE and sorafenib provided a longer TTP and MST in patients with unresectable HCC in comparison of TACE alone. Sorafenib is a multikinase inhibitor that blocks the VEGF receptors and intracellular signaling pathways such as the Raf-MEK dependent pathways[2]. In contrast, although TACE is an effective therapy for unresectable HCCs, its arterial embolization increases the expression of VEGF, leading to tumor angiogenesis, which results in recurrence and/or metastasis[12-14]. It has therefore been assumed that the combination therapy of TACE and sorafenib would improve the prognosis of unresectable HCC by overcoming the TACE-induced increase in VEGF through the pharmacological effects of sorafenib

Table 2. Sorafenib-related adverse effects (number of cases)

Hand-foot skin reaction	6 cases (grade 1, $n=1$, grade 2, $n=4$, grade 3, $n=1$)
Hand-foot skin reaction and anorexia	1 case* (grade 3)
Hypertension	1 case
Liver enzyme elevation And anorexia	1 case*

*These cases were excluded from the data analysis because the administration of sorafenib was stopped due to adverse events.

on the VEGF receptors and intracellular signaling pathways related to tumor cell proliferation[15]. Unfortunately, however, several large-scale clinical trials and meta-analyses failed to show the superiority of the combination therapy to TACE alone[6,7,9]. This might be attributed, at least in part, to the prolonged time between the first TACE procedure and the administration of sorafenib[8,9]. This idea prompted us to conduct the present study in which the administration of srafenib was started soon after the patient recovered from the adverse events due to the initial TACE procedure. Thus, it may be reasonable to speculate that the short time lag between the initial TACE procedure and the initiation of sorafenib treatment in the present study contributed to the better prognosis of Group C.

Although sorafenib is an effective systemic therapy for HCC, it is associated with a considerably high rates of adverse events[16]. The adverse events include gastrointestinal symptoms (*i.e.*, diarrhea and anorexia), hand-foot skin reactions and hypertension. Sorafenib-related adverse effects were observed in all of patients in the present study (Table 2). Among 9 cases that were primarily treated with the combination therapy during this study period, unfortunately, 2 cases had to be excluded when sorafenib was discontinued due to adverse events. One was due to liver enzyme elevation ; the other was due to severe anorexia and a hand-foot-skin reaction. In contrast, none of the patients in Group T were excluded from the study due to severe adverse events ; this is consistent with previous reports[17]. Thus, prophylaxis and the early treatment of sorafenib-related adverse events should always be kept in mind by physicians in order to improve the outcomes of the combination therapy of TACE and sorafenib in patients with HCC.

In the current study, we demonstrated that the number of TACE procedures in Group C was significantly higher than that in Group T (Figure 3). We believe that this factor was strongly associated with the increased MST in group C. Even in the previous studies that failed to show the superior survival of patients receiving the combination therapy group of TACE and sorafenib in comparison to TACE alone, the TTP of the combination therapy group was shown to be longer[6,7]. Nevertheless, the number of TACE procedures in the combination therapy group of the present study (average : 5.6 times) was much higher than that in previous studies (average : 1.0-2.0 times)[18]. As noted above, the early initiation of sorafenib after the initial TACE procedure might have helped to increase the number of TACE procedures in the present study ; this is in turn might have led to the increased MST. Furthermore, it is noteworthy that even though the patients in Group C had significantly greater numbers of tumors than those in Group T, the TTP and MST were both markedly longer in group C. These data strongly suggest that our combination therapy protocol has the potential to be the first choice of treatment for unresectable HCC.

The present study is associated with some limitations. First, this was a retrospective study that was performed at a single institution. Second, the number of cases, especially in group C, was small. A further prospective study should be performed with a lager study population.

In conclusion, we showed that in patients with unresectable HCC, the combination therapy of TACE and sorafenib was associated with a better prognosis in comparison to TACE alone. These data provide a better perspective for the therapeutic strategies for unresectable HCCs.

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