

Hemodynamic Changes on Cone-Beam Computed Tomography during Balloon-Occluded Transcatheter Arterial Chemoembolization Using Miriplatin for Hepatocellular Carcinoma: A Preliminary Study

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Keywords

Miriplatin · Cone-beam CT · Balloon-occluded transcatheter arterial chemoembolization · Pixel · CT value

Abstract

Background/Aim: Balloon-occluded transcatheter arterial chemoembolization (B-TACE) using miriplatin (MPT) is anticipated as a new strategy for hepatocellular carcinoma (HCC). This study was aimed at evaluating the hemodynamic changes with/without balloon occlusion of the hepatic artery, correlation of cone-beam CT (CBCT) pixels, and CT value after B-TACE for HCC. **Methods:** A total of 52 patients with HCC, who underwent B-TACE using MPT in addition to the balloon-occluded CBCT hepatic arteriography, were studied. **Results:** After balloon occlusion, CBCT pixel values increased in 37 lesions, whereas it decreased in 15 lesions. Intratumoral CT values after B-TACE were lower with decreased CBCT pixel values than with increased CBCT pixel values. **Conclusion:** Hemodynamic changes on CBCT during balloon occlusion can be used to predict the efficacy of B-TACE using MPT.

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Introduction

Cone-beam CT (CBCT) using a flat panel detector (FPD) is an imaging methodology of CT, which is different from conventional CT [1].

CBCT has various artifacts that are not available in conventional CT. Currently, CBCT technology has improved with artifact reduction, and is already well-established in the diagnosis of hepatocellular carcinoma (HCC) [2].

Miriplatin (MPT, Miripla; Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan) is a specifically designed drug for transarterial chemoembolization (TACE) of HCCs [3]. Balloon-occluded TACE (B-TACE) is a modification of the treatment strategy that is anticipated to improve drug concentration in the tumor [4].

The degree of lipiodol accumulation in a tumor post-TACE correlates with the risk of local recurrence. We have previously reported that the Hounsfield unit value of a tumor obtained from conventional CT immediately after B-TACE with MPT is predictive of the recurrence risk [5].

However, to the best of our knowledge, only a few reports have investigated the correlation of hemodynamics between balloon occlusion CBCT and conventional CT values immediately after B-TACE. The present study is aimed at evaluating the hemodynamic changes with/without balloon occlusion of the hepatic artery and correlation of CT value after B-TACE for HCC.

Methods

Patients and Methods

Study Cohort

A total of 52 patients (52 nodules) with HCC who underwent B-TACE using MPT (Miripla; Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan) at Saiseikai Niigata Daini Hospital between December 2015 and May 2017 were included in this study.

All patients received a comprehensive evaluation by dynamic contrast CT prior to treatment. The study exclusion criteria were: (1) tumor size ≥ 5 cm; (2) intentionally incomplete TACE because of tumor infiltration; (3) ≥ 4 -month interval between TACE and initial CT during follow-up observation; (4) no CT done during follow-up observation; and (5) nodules with locoregional therapy such as percutaneous ethanol injection, microwave coagulation therapy, laser ablation, and radiofrequency ablation as additional treatment, (6) extrahepatic metastasis of HCC, and (7) other malignancies.

TACE Protocol and CBCT Imaging

In all cases, vascular access was achieved using the Seldinger technique. Briefly, the femoral artery was punctured, and a 5-Fr introducer was inserted followed by a 5-Fr catheter. A microballoon catheter (Attendant, Terumo, Tokyo, Japan or Logos, Piolax, Kanagawa, Japan) was then advanced into the selective or super-selective branches of the tumor's feeding arteries through a 5-Fr catheter. The microballoon catheter was introduced over a 0.014-inch guide wire (Chikai; Asahi Intec, Aichi, Japan). The tip of the microballoon catheter was positioned in the tumor's feeding artery. CBCT using an Allura Clarity FD20 (Philips, Best, The Netherlands) hepatic arteriography (CB-CTHA) was performed before and after the inflation of the balloon. Six hundred projection images with X-ray parameters of tube voltage 117–123 kV, pulse width 5–10 ms, and tube current 50–325 mA were obtained by 5.2-s acquisitions with 240° C-arm rotation around the patient. The FPD was used for image acquisition, which has a focal spot-detector distance of 120 cm with a 19-inch field of view. The acquisition images by FPD were automatically transferred to an Xtravision workstation (Philips) and reconstructed with artifact reduction. CB-CTHA with/without balloon occlusion was performed for areas containing HCC nodule.

The first CB-CTHA scan started 7–10 s after the initiation of a transcatheter hepatic arterial injection of 5–15 mL of nonionic contrast material (iopamidol, iopamiron® 150 iodine, 150 mg I/mL; Bayer HealthCare, Osaka, Japan) at a speed of 0.5–1.0 mL/s using the automated power injector, and the second scan started 30 s after the first scan ended.

The appropriate injection rate for CB-CTHA was determined by the maximum injection rate (which was basically dependent on the vessel caliber) that would not cause a backward flow of contrast

material on the hepatic arteriography. The injection rate was the same before and after the inflation of the balloon. The balloon was inflated to a diameter 5–10% larger than that of the occluded artery. Subsequently, MPT was prepared by mixing 60 or 120 mg (1 or 2 vials) of MPT hydrate in 3 or 6 mL of lipiodol. The maximum dose of MPT was limited to 120 mg.

MPT infusion was performed after balloon occlusion. MPT infusion was continued under balloon occlusion until HCC was filled with MPT or portal venous branches were beginning to be filled with MPT. Fluoroscopy and digital subtraction angiography during B-TACE procedures observed whether any limitation of MPT inflow into non-tumorous liver parenchyma and dense accumulation in HCC nodule were present, and whether or not anastomotic vessels with collateral artery were present. Then the balloon was deflated.

Conventional CT was performed immediately after the B-TACE. All conventional CT images were obtained using a multi-detector-row helical CT scanner (Aquilion PRIM; Toshiba Medical Systems, Tokyo, Japan). The parameters for scanning were as follows: collimation, 1 mm; reconstruction, 3 mm; pitch, 15; amperage, 300 mA s; kilo voltage, 120 kVp. The images were transferred to the PACS as DICOM data.

Using the EV Insite net software, regions of interest were placed on both CBCT and conventional CT DICOM images, adjusted to 1-mm slice thickness, at the same position. The automatically generated average pixels were recorded.

Ethics Statement

The study was approved by the Ethics Committee of Saiseikai Niigata Daini Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved, and written informed consent was obtained from all participating patients.

Statistical Analysis

Variable data are expressed as mean \pm SD. Categorical variables were compared using χ^2 test or Fisher's exact test, where appropriate. Continuous variables were compared using the independent sample Student's *t* test or one-way repeated analysis of variance. Values of $p < 0.05$ were considered to indicate statistically significant differences. Statistical processing was performed using Stat-View version 5.0 software (SAS Institute, Cary, NC, USA).

Results

The study included 52 patients (40 males and 12 females; mean age 72.32 ± 7.78 years), with a total of 52 nodules that were treated with B-TACE using MPT. The average diameter of the nodules on conventional CT was 27.69 ± 6.82 mm (Table 1). The nodules were located at segment S1 ($n = 2$), S2 ($n = 3$), S3 ($n = 3$), S4 ($n = 7$), S5 ($n = 6$), S6 ($n = 7$), S7 ($n = 5$), and S8 ($n = 19$).

CBCT pixel values with balloon occlusion were significantly higher than those without balloon occlusion ($p = 0.002$; Fig. 1). CBCT pixel values increased after balloon occlusion in 37 of the 52 tumors, whereas it decreased after balloon occlusion in 15 tumors. The clinical

Table 1. Baseline characteristics of the study population

Demographic variables	Mean ± SD	Range
Age, years	72.32±7.78	50–89
Gender, male:female	40:12	
Etiology (HBV/HCV/NonHBVNonHCV)	9/26/17	
Size, mm	27.69±6.82	10–40
Location (S1/2/3/4/5/6/7/8)	2/3/3/7/6/7/5/19	
Cone-beam CT (pixel)	185.01±98.17	64.0–626.4
Balloon cone-beam CT (pixel)	237.72±179.91	94.6–1,198.1
Post-CT value (HU)	340.36±215.74	122.1–109.2

HBV, hepatitis B virus; HCV, hepatitis C virus; HU, Hounsfield unit.

Table 2. Clinical features according to pixel changes after balloon occluded cone-beam CT angiography

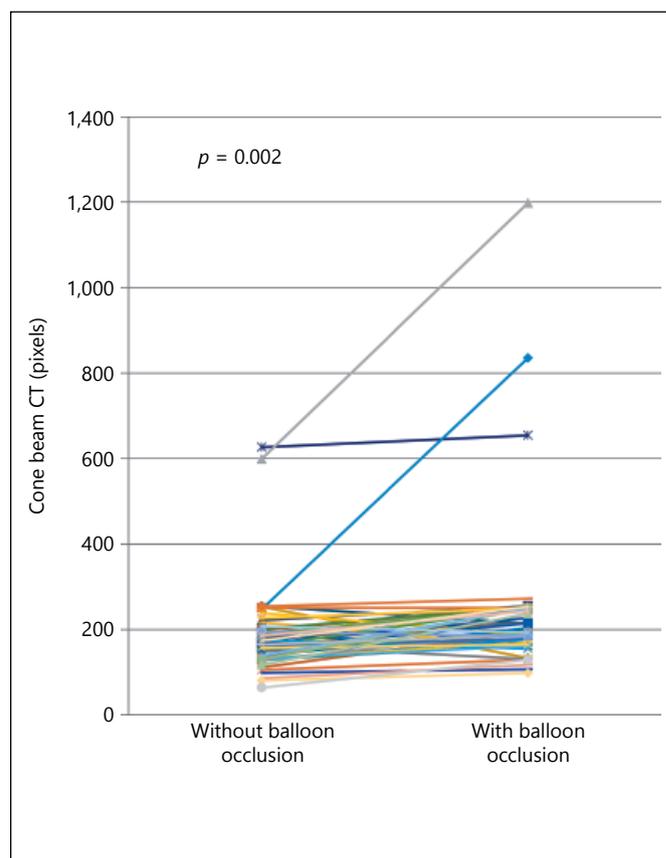
Demographic variables	Decreased	Increased	<i>p</i> value
Age, years	71.40±9.65	72.70±7.01	0.589
Gender, male:female	13:2	27:10	0.288
Etiology (HBV/HCV/ nonHBV vs. nonHCV)	1/6/8	8/20/9	0.126
Size, mm	26.00±5.73	28.37±7.17	0.259
Location (S1/2/3/4/5/6/7/8)	0/2/0/2/1/3/1/6	2/1/3/5/5/4/4/13	0.746
Cone-beam CT (pixel)	175.34±55.53	188.92±111.35	0.656
Balloon cone-beam CT (pixel)	162.93±42.15	268.92±204.67	0.048
Post-CT value (HU)	208.26±62.66	393.91±232.78	0.003

HBV, hepatitis B virus; HCV, hepatitis C virus; HU, Hounsfield unit.

features of the nodules with increased or decreased pixel values are given in Table 2. There was no significant difference at baseline between groups with increased and decreased pixel values; however, the CT value after B-TACE in the increased pixel group was significantly higher than that in the decreased pixel group ($p = 0.003$).

Discussion

TACE was established for the treatment of HCC when surgical resection [6] or other locoregional treatments [7–13] is not indicated. High concentrations of the drug-delivery vehicle lipiodol in the tumor at the time of treatment are associated with lower risks of local tumor recurrence [14]. MPT (cis-[[((1R, 2R)-1, 2-cyclohexanediamine-N, N0)bis(-myristato)]-platinum(II) monohydrate; Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan) is a novel lipophilic cisplatin derivative that can be suspended in lipiodol [3, 15, 16].

**Fig. 1.** Changes in cone-beam CT pixels with and without balloon occlusion of the hepatic artery.

Theoretically, MPT is a good agent in terms of its higher solubility, stability in lipiodol, and gradual release within the tumor.

However, a recent study reported that the local recurrence rate was significantly higher for MPT than for epirubicin with mitomycin C in lipiodol-based superselective TACE for HCC [17].

This inferior local control with MPT can be attributed to its higher viscosity. Various methods of administration with MPT are currently being studied to increase its therapeutic efficacy. Irie et al. [4] revealed that dense accumulation in the HCC nodule could be achieved by B-TACE with doxorubicin and mitomycin C.

We previously reported that B-TACE with MPT achieved relatively good local control of HCC (local recurrence rate, 11.1% at 6 months and 26.2% at 12 months) [5]. The mechanism of improved local control can be explained by the presence of anastomotic vessels, viscosity of lipiodol emulsion, and difference in size between the peripheral vessels in normal parenchyma and the vessels

feeding into the HCC. Moreover, we concluded that the plain CT value immediately after B-TACE with MPT is a predictive factor for local recurrence [5].

However, some lesions were not responsive to B-TACE. Currently, CBCT technology has improved with artifact reduction and is already well-established in the diagnosis of HCC [2]. Furthermore, it is possible that CBCT can be successfully used to predict HCC tumor outcome post-TACE [18].

This study was aimed at evaluating the hemodynamic changes with/without balloon occlusion of the hepatic artery and correlation of CT values after B-TACE for HCC.

We speculated that CBCT with/without balloon occlusion can provide useful information for the analysis of hemodynamic changes.

In this study, CB-CT pixel values with balloon occlusion were significantly higher than those without balloon occlusion. However, CB-CT pixel values after balloon occlusion decreased in some cases.

In the increased group, postoperative CT value was clearly higher, and local recurrence may be suppressed. By performing CB-CT before and after bal-

loon occlusion, it may be possible to predict the effect of B-TACE using MPT. Whereas lower CB-CT pixel values after balloon occlusion groups may be considered to be ineffective, there is a need to consider other strategies.

In conclusion, following balloon occlusion, intratumoral arterial flow can change, presumably due to a collateral pathway. B-TACE for HCC lesions showing decreased pixel values after balloon occlusion CBCT may have a poor short-term therapeutic effect compared to those with increased pixel values.

Disclosure Statement

The authors declare that no conflict of interest exists.

Financial Disclosure

The authors declare that they do not have a current financial arrangement or affiliation with any organization that may have a direct interest in their work.

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