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Efficacy of Transarterial Chemoembolization with Drug-Eluting Beads in Hepatocellular Carcinoma: A Single-Center Experience

Hepatosellüler Karsinomda İlaç Yüklenebilir Mikroküreler ile Yapılan Transarteriyel Kemoembolizasyonun Etkinliği: Tek Merkez Deneyimi

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ABSTRACT

Aim: The aim of this study was to evaluate the efficacy of transarterial chemoembolization (TACE) with drug-eluting beads in hepatocellular carcinoma (HCC).
Material and Methods: Twenty-nine patients with HCC who were treated with TACE with drug-eluting beads between 2019 and 2021 were included in the study. The success of the TACE procedure was evaluated using pre- and post-operative contrast-enhanced computed tomography/magnetic resonance images. Patient characteristics, embolizing-bead sizes, procedure-related complications, and pre- and post-procedure alpha-fetoprotein (AFP) levels were recorded.
Results: The mean age of the patients was 65.6±10.4 years, and the objective response rate was 17.2% (5/29). 100-300 μm particles were used in 11 (37.9%) patients, and 300-500 μm particles were used in 18 (62.1%). The median target lesion number was 1 (range, 1-6). Six (20.7%) patients had non-target lesions. There were newly developed lesions in four (13.8%) patients. A significant decrease was found in the median target lesion size after (41; range, 0-116 mm) the procedure compared to the pre- (42; range, 22-188 mm) procedure ($p<0.001$). A significant difference was found between the median AFP levels before (343; range, 1.44-2000 ng/mL) and after (52; range, 0.95-1435 ng/mL) the procedure ($p<0.001$).
Conclusion: Since most patients with HCC are diagnosed in the intermediate stage, curative treatment is not possible. TACE is an important treatment option for the local control of the disease in this patient group. However, the success of TACE treatment may vary depending on the cancer stage, number of patients, follow-up period, and type and size of the microsphere used.
Keywords: Hepatocellular carcinoma; transarterial chemoembolization; drug-eluting beads.

ÖZ

Amaç: Bu çalışmanın amacı hepatosellüler karsinomda (HCC) ilaç salınımlı mikroküreler ile yapılan transarteriyel kemoembolizasyon (TAKE) tedavisinin etkinliğini değerlendirmektir.
Gereç ve Yöntemler: 2019 ve 2021 tarihleri arasında ilaç salınımlı mikroküreler ile TAKE uygulanan 29 HCC'li hasta çalışmaya dahil edildi. TAKE işleminin başarısı işlem öncesi ve sonrası kontrastlı bilgisayarlı tomografi ve manyetik rezonans görüntüleri ile değerlendirildi. Hasta karakteristikleri, embolizasyon için kullanılan mikroküre boyutları, işleme bağlı komplikasyonlar ve işlem öncesi ve sonrası alfa fetoprotein (AFP) düzeyleri kaydedildi.
Bulgular: Hastaların yaş ortalaması 65,6±10,4 yıldı ve objektif yanıt oranı %17,2 (5/29) idi. 11 (%37,9) hastada 100-300 μm ve 18 (%62,1) hastada 300-500 μm boyutlarında partikül kullanılmıştı. Ortanca hedef lezyon sayısı 1 (aralık, 1-6) idi. Altı (%20,7) hastada hedef olmayan lezyon mevcuttu. Dört (%13,8) hastada yeni gelişen lezyon mevcuttu. İşlem sonrası ortanca hedef lezyon boyutunda (41; aralık, 0-116 mm) işlem öncesi (42; aralık, 22-188 mm) ile karşılaştırıldığında anlamlı bir azalma olduğu saptandı ($p<0,001$). Ayrıca, işlem öncesi (343; aralık, 1,44-2000 ng/mL) ve işlem sonrası (52; aralık, 0,95-1435 ng/mL) ortanca AFP değerleri arasında anlamlı bir farklılık saptandı ($p<0.001$).
Sonuç: HCC hastalarının büyük bir kısmı intermediate evrede teşhis edildiğinden küratif tedavileri mümkün değildir. Bu hasta grubunda TAKE, hastalığın lokal kontrolünde önemli bir tedavi seçeneğidir. Bununla birlikte, TAKE tedavisinin başarısı kanser evresi, hasta sayısı, takip süresi ve kullanılan mikrokürenin tipi ve boyutuna göre değişkenlik gösterebilir.
Anahtar kelimeler: Hepatosellüler karsinom; transarteriyel kemoembolizasyon; ilaç salınımlı mikroküreler.

INTRODUCTION

Liver cancer is the sixth most frequently diagnosed cancer, and ranks fourth in cancer-related deaths (1). Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver (2).

The surgical treatment of liver tumors is an option with curative potential. However, only 20% of patients are suitable for surgical treatment (3). Most liver malignancies cannot be treated surgically due to the presence of comorbidities, multiple metastases, anatomical localization where resection is not possible, insufficient functional liver capacity, and tumor recurrence (4,5). Locoregional therapies are applied to patients who are not suitable for surgical treatment. Transarterial chemoembolization (TACE) and ablation are the most preferred locoregional therapy methods in this field (6-8). In HCC, the Barcelona Clinic Liver Cancer (BCLC) staging and treatment algorithm are used to guide treatment based on the tumor stage, liver functional status, physical condition, and cancer-related symptoms of patients. TACE treatment is applied in BCLC stage B HCC and causes necrosis in the tumor with arterial embolization and death of tumor cells through the cytotoxic effects of the chemotherapeutic drugs used. TACE can inhibit tumor progression and improve survival; therefore, it is considered a palliative treatment for BCLC stage B HCC (9). The current study aimed to evaluate the efficacy of TACE treatment with drug-eluting beads in HCC.

MATERIAL AND METHODS

After obtaining approval from the local ethics committee (Sakarya University, 02.02.2022, 102075), 29 patients with BCLC stage B HCC who were referred to our clinic at Sakarya University Training and Research Hospital for TACE treatment between 2019 and 2021 were retrospectively included in the study. The exclusion criteria were determined as uncorrected coagulopathy and pregnancy. Response to treatment was evaluated with contrast-enhanced computed tomography/magnetic resonance (CT/MR) images taken before (Figure 1.A) and after the procedure. Drug-eluting bead sizes, pre- and post-procedure alpha-fetoprotein (AFP) levels, and procedure-related complications were recorded.

TACE Procedure

With the patient under local anesthesia, a 5F vascular sheath was placed in the right common femoral artery under ultrasound guidance. Then, angiograms were obtained from the celiac artery and superior mesenteric artery to determine the origin of the hepatic artery with a 0.035" guide wire and Cobra/Simmons 1 (Tempo, Cordis, UK) catheter. After the celiac artery/superior mesenteric artery was catheterized, the origin of the feeding arteries of the lesions was determined on the angiograms (Figure 1.B). Subsequently, a microcatheter (Renegade, Boston Scientific, USA) was super selectively advanced to the feeding arteries of the tumor. A mixture of doxorubicin, drug-eluting embolizing particles (DC Bead, Boston Scientific, USA), and iohexol, a low-osmolarity contrast agent (Opaxol, Opakim, Turkey), was administered via the microcatheter. Embolizing injection was performed away from the origin of the gastroduodenal, right gastric, and cystic arteries. In order to prevent off-target embolization, the embolizing particle was injected slowly, and the procedure was terminated when stagnation developed (Figure1.C).

Analgesic and antiemetic treatments were administered during and/or after the procedure. The patients were non-invasively monitored with oxygen saturation and blood pressure measurements and electrocardiography throughout the procedure.

Imaging and Follow-up

Before and after (Figure 1.D) the TACE procedure, dual-phase (arterial and portal venous phase) contrast CT/MR images of the liver were obtained with the same protocol. Treatment efficacy was evaluated with contrast-enhanced CT/MR imaging at the first month.

The modified response evaluation criteria in solid tumors (mRECIST) criteria were used to assess the patients' response to treatment. For this purpose, HCC lesions were categorized as target, non-target, and newly developed. For a lesion to be classified as a target lesion, it should be suitable for repeated measurements, show an arterial enhancement pattern, and have at least one diameter that is ≥1 cm (10). The response of target and non-target lesions to TACE treatment according to the mRECIST criteria is summarized in Tables 1 and 2, respectively. The presence of a newly developed lesion of ≥1 cm with arterial hypervascularity and contrast washout in the portal venous or late phase indicates HCC without histopathology (10). If the newly developed lesions did not meet these criteria, it was decided whether HCC was present according to the follow-up examinations. The overall response of the patients to TACE therapy was determined by evaluating the target, non-target, and newly developed lesions together (Table 3).

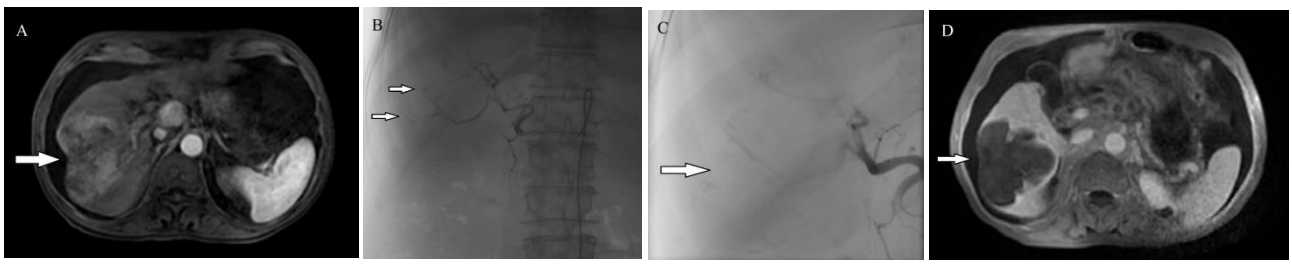

Figure 1. Radiological images of a 78-year-old male patient **A)** Contrast-enhanced abdominal magnetic resonance (MR) image shows hepatocellular carcinoma (HCC) with a diameter of 87 mm in the liver with contrast enhancement in the arterial phase. **B)** Angiography image shows the tumoral staining of HCC before embolization **C)** Angiography image after transarterial chemoembolization with drug-eluting beads shows occlusion and stagnation in the feeder artery of the tumor **D)** Contrast-enhanced MR image taken at the first postoperative month shows no contrast enhancement in the tumoral area, and the appearance is consistent with complete response

Table 1. Response of target lesions to transarterial chemoembolization (TACE) treatment according to the modified response evaluation criteria in solid tumors (mRECIST) criteria (10)

Treatment Response	Definition
Complete response	Disappearance of intra-tumoral arterial enhancement in all target lesions
Partial response	≥30% reduction in the sum of the longest diameters of all target lesions showing arterial enhancement
Stable disease	Cases that cannot be categorized as having partial response or progressive disease
Progressive disease	≥20% increase in the sum of the shortest diameters of all target lesions showing arterial enhancement

Table 2. Response of non-target lesions to transarterial chemoembolization (TACE) treatment according to the modified response evaluation criteria in solid tumors (mRECIST) criteria (10)

Treatment Response	Definition
Complete response	Disappearance of intra-tumoral arterial enhancement in all non-target lesions
Incomplete response/stable disease	Persistence of intra-tumoral arterial enhancement in one or more non-target lesions
Progressive disease	Emergence of one or more new lesions and/or definite progression of existing non-target lesions

Table 3. Overall response of patients with hepatocellular carcinoma (HCC) to transarterial chemoembolization (TACE) treatment according to the modified response evaluation criteria in solid tumors (mRECIST) criteria (10)

Target Lesion	Non-target Lesion	Newly developed Lesion	Overall Response
CR	CR	Absent	CR
CR	IR/SD	Absent	PR
PR	No PD	Absent	PR
SD	No PD	Absent	SD
PD	Any category	Any category	PD
Any category	PD	Any category	PD
Any category	Any category	Present	PD

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, IR: incomplete response

Statistical Analysis

Statistical analysis was performed using MedCalc (ver.12, Ostend, Belgium) software package. For the statistical analysis, categorical variables were presented as numbers and percentages, and continuous variables as median, quartiles, and minimum-maximum values for descriptive findings. Continuous variables were compared with Wilcoxon test according to their conformance to a normal distribution determined with the Shapiro-Wilk test. The statistical significance level was accepted as $p<0.05$.

RESULTS

Twenty-four (82.8%) patients were male and five (17.2%) were female. The mean age of the patients was 65.6±10.4 years. Before the TACE procedure, surgery was performed in two (6.9%) patients and microwave ablation (MWA) in three (10.3%). 100-300 μm particles were used in 11 (37.9%) patients and 300-500 μm particles in 18 (62.1%). The median number of target lesions was 1 (range, 1-6). Six (20.7%) patients had non-target lesions, and four (13.8%) had a newly developed lesion. The target lesion and overall treatment response are presented in Table 4. The objective response rate, which represents the percentage of patients with a complete or partial response, was determined as 17.2% (5/29).

A significant difference was found between the median AFP values before (343; range, 1.44-2000 ng/mL) and after (52; range, 0.95-1435 ng/mL) the procedure ($p<0.001$). In addition, there was a significant decrease in the median target lesion size after (41; range, 0-116 mm) the procedure compared to the pre- (42; range, 22-188 mm) procedure ($p<0.001$; Table 5).

Mild postembolization syndrome, which causes abdominal pain and nausea/vomiting, was observed in eight (27.6%) of the patients. Liver abscess developed in one (3.4%) patient after embolization.

Table 4. Treatment response of target lesions and overall treatment response

	Target Lesion Response	Overall Treatment Response
Complete response	1 (3.4%)	1 (3.4%)
Partial response	5 (17.2%)	4 (13.8%)
Stable disease	20 (69%)	17 (58.6%)
Progressive disease	3 (10.4%)	7 (24.2%)

Table 5. Serum AFP level and target lesion size comparison before and after the procedure

	Pre-procedure	Post-procedure	p
AFP (ng/mL)	343 (20.25-715.25) [1.44-2000]	52 (10.85-220) [0.95-1435]	**<0.001**
Target lesion size (mm)	42 (32.75-90.25) [22-188]	41 (22-79.25) [0-116]	**<0.001**

AFP: alpha-fetoprotein, descriptive statistics were reported as median (1^{st} quartile – 3^{rd} quartile) [minimum-maximum]

DISCUSSION

In this study, the efficacy of TACE therapy in BCLC stage B HCC was evaluated. In the literature, it has been reported that in the absence of vascular invasion and extrahepatic tumor spread, TACE may improve one- and two-year survival in patients with HCC who are not suitable for curative treatment (11). Conventional TACE involves the injection of a mixture of a chemotherapeutic agent and iodized oil. Many studies are being conducted to increase the efficacy of locoregional therapies and reduce the systemic toxicity of chemotherapeutic drugs. Drug-eluting beads are among the products developed for this purpose (11). In vitro studies and animal experiments have proven that TACE administered with drug-eluting beads is associated with a mild transient increase in liver enzymes, reduced plasma doxorubicin levels, and increased tumor necrosis (12-14). Therefore, in the current study, TACE was performed with drug-eluting beads (DC Beads, Boston Scientific, USA).

There are studies comparing the treatment efficacy and complication rates according to the size of drug-eluting beads (15). Higher coagulation necrosis and complete response rates, longer overall survival, less fibrosis, and postembolization syndrome have been reported in embolization procedures performed with 100-300 μm particles compared to those undertaken with larger particles (15). However, due to the risk of severe necrosis in normal liver tissue, advanced embolization with very small particles should be avoided (11). While no significant difference has been shown between large and small size particles in terms of drug release, it has been reported that small beads have a higher drug-eluting capacity due to their high surface area/volume ratio (15). Many factors such as tumor volume, size of the artery feeding the tumor, and tumor characteristics should be considered in the selection of the bead size to be used. In addition, the presence of an arteriovenous shunt is very important in this decision. Therefore, a careful examination of angiographic images is necessary before embolization in order to prevent serious complications. In the current study, the size of the drug-eluting beads used was 100-300 μm in 11 (37.9%) patients and 300-500 μm in 18 (62.1%).

The efficacy of TACE also depends on the arterial blood supply to the tumor, tumor size, and ultraselective positioning of the embolizing catheter, and it is almost impossible to achieve complete tumor necrosis with TACE alone. Residual tumor cells may cause local recurrence and distant metastasis (16,17). Studies have shown that the combination of TACE and local ablative treatments is much more successful than the use of either method alone (18,19). The synergistic effect of the combination of TACE and MWA/radiofrequency ablation (RFA) can be explained as follows: With TACE, hepatic arterial blood flow is decreased, the heat sink effect of vascular structures in local ablative treatments is reduced, and the thermal efficacy of MWA/RFA and the attainable intra-tumor temperature level are increased. Similarly, chemotherapeutic drugs used in TACE can increase the thermal sensitivity of tumor cells and thermal conductivity of MWA (20-22). Combined therapies can be used as an alternative method for the successful eradication of the tumor and maximum preservation of liver function (23). In the current study, before the TACE procedure, surgery was performed in two (6.9%) patients, and MWA was applied to three (10.3%), and TACE was planned when recurrence was observed. There was a significant decrease in the AFP values of the patients and the sum of the diameters of the target lesions compared to the pre-procedure evaluation. The objective response rate was determined as 17.2%, which was lower than previously reported rates of 51.6% (24) and 66.6-76.8% (25). These differences in clinical results can be due to various factors, such as the cancer stage, number of patients, follow-up period, and type and size of the beads used (25).

For TACE performed with drug-eluting beads in patients with HCC, the rate of major complications has been reported as 1.6-7.2% and that of minor complications as 30.2-67.6% (25). In the current study, mild postembolization syndrome, which causes abdominal pain and nausea/vomiting, was observed in 27.6% of the patients. In addition, liver abscess developed in one (3.4%) patient after embolization. A drainage catheter was placed in the abscess under ultrasound guidance, and the patient was treated with appropriate antibiotic therapy.

The limitations of this study can be listed as limited number of participants, its single-center nature, short follow-up period, and retrospective design.

CONCLUSION

Since most patients with HCC are diagnosed in the intermediate stage, curative treatment is not possible. TACE seems to be an important treatment option in the local control of the disease in this patient group. However, the success of TACE may vary depending on the cancer stage, number of patients, follow-up period, and type and size of the beads used. It is predicted that the newly developed agents and drug-eluting beads will increase the success of TACE treatment, and to achieve this, further large-scale and long-term studies are needed.

Ethics Committee Approval: The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (02.02.2022, 102075).

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