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The Effect of Transarterial Y-90 Microsphere Treatment on Biochemical Parameters in Liver Tumors

Karaciğer Tümörlerinde Transarteriyel Y-90 Mikroküre Tedavisinin Biyokimyasal Parametreler Üzerine Etkisi

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ABSTRACT

Introduction: The aim of this study was to evaluate the effect of yttrium-90 (Y-90) microsphere transarterial radioembolization (TARE) treatment on early and late biochemical parameters and to determine the appropriate and effective follow-up schedule in the patients and to determine the biochemical parameters to be considered.

Methods: A total of 106 patients with histopathologically verified primary or metastatic unresectable liver tumors that were treated with TARE at a single institution between 2016-2018 were retrospectively scanned from database. Of these patients, 27 patients (18 male and 9 female patients; mean age: 61.5±10.5 years, range: 40-77 years) were included in the study. It was investigated whether there was a significant difference between the biochemical parameters just before the treatment, on the 10th day and 3 months after the treatment.

Results: Statistically significant difference was observed only between pre-treatment albumin (albumin 1) and 10th day albumin (albumin 2), and between pre-treatment albumin (albumin 1) and 3rd month albumin (albumin 3) levels ($p<0.05$). There was no statistically significant difference between other biochemical parameters ($p>0.05$).

Conclusion: Albumin value was the most sensitive biochemical parameter in TARE treatment with Y-90 microsphere. It is of great importance that albumin value is frequently followed carefully in these patients.

Keywords: Y-90 microsphere, radio-embolization, side effect, liver

ÖZ

Amaç: Yitriyum-90 (Y-90) mikroküre ile transarteriyel radyoembolizasyon (TARE) tedavisinin erken ve geç biyokimyasal parametreler üzerine etkisinin araştırılarak tedavi edilen hastalarda uygun ve etkili takip planının yapılması ve özellikle dikkat edilmesi gereken biyokimyasal parametrelerin belirlenmesi amaçlanmıştır.

Yöntemler: Yerel veri tabanınından tek merkezde 2016-2018 yılları arasında primer veya metastatik inoperabl karaciğer tümörü histopatolojik olarak kanıtlanmış toplam 106 hastaya TARE tedavisi uygulandığı saptandı. Bu hastaların 27 tanesinin (18 erkek, 9 kadın; ortalama yaş: 61,5±10,5 yıl, aralık: 40-77 yıl) tedavi öncesi, erken ve geç tedavi sonrası tüm biyokimyasal parametrelerine ulaşılarak çalışmaya dahil edildi. Tedaviden hemen önce, tedavi sonrası 10. gün ve 3. ay biyokimyasal parametreler arasında anlamlı farklılık olup olmadığı araştırıldı.

Bulgular: İstatistiksel anlamlı farklılık sadece tedavi öncesi albümin (albümin 1) ile tedavi sonrası 10. gün takip albümin (albümin 2) değerleri ile tedavi öncesi albümin (albümin 1) ile tedavi sonrası 3. ay takip albümin (albümin 3) değerleri arasında saptandı ($p<0,05$). Bakılan diğer biyokimyasal parametreler arasında ise istatistiksel herhangi bir anlamlı fark saptanamadı ($p>0,05$).

Sonuç: Y-90 mikroküre ile TARE tedavisinde en hassas biyokimyasal parametrenin albümin değeri olduğu saptanmıştır. Tedavi uygulanan hastalarda albümin değeri takiplerinin sıklıkla ve dikkatle takibi büyük önem taşımaktadır.

Anahtar Kelimeler: Y-90 mikrosfer, radio-embolizasyon, yan etki, karaciğer

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Introduction

Liver cancer, including primary hepatocellular carcinoma and intrahepatic cholangiocarcinoma (comprising 10-15% of cases) as well as other rare types, is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide in 2018, with about 841.000 new cases and 782.000 deaths annually (1). In addition, liver is a frequent site of metastasis for many common malignancies such as breast and colon (2-4). The prognosis of unresectable liver cancer is poor (5). Treatment options include chemotherapy, transarterial chemoembolization, regional radiotherapy, radiofrequency ablation, transarterial radioembolization (TARE) and transplantation (5).

In recent years, TARE with yttrium-90 (Y-90) microspheres has become a safe treatment option for unresectable primary and metastatic liver malignancies (6-9). It may also be preferred as a bridge prior to resection, radiofrequency ablation and liver transplantation (7). TARE may be helpful in the management of advanced liver malignancies (10-13). Its palliative role through tumor necrosis and delaying progression has also been shown (6).

TARE is an internal, local, highly selective radiation therapy that has minor embolization effects (14). This treatment modality has less side effects and complications when compared to other local and systemic therapies of liver malignancies with the help of different arterial access to tumor tissue (6,14). In order to decide TARE treatment, complete blood count and biochemical tests including liver and renal function (albumin, total bilirubin, aspartate amino transferase, alanine amino transferase, blood urea nitrogen and creatinine) should be analyzed. Biochemical tests, clinical status of patients and possible side effects should be checked regularly after treatment (14). The most frequent side effects of the treatment occur immediately after treatment and they usually do not need further treatment. On the other hand, rare serious side effects and complications can be observed mostly 3 months following TARE (15,16).

The aim of this study was to evaluate the early and late effects of TARE treatment on biochemical parameters and to determine the appropriate follow-up schedule.

Methods

Patient Population and Data Collection

The study protocol was approved by the İstanbul Training and Research Hospital Local Ethics Committee as a retrospective study (decision no: 1584, date: 21.12.2018). A total of 106 patients with histopathologically verified primary or metastatic unresectable liver tumors that were treated with TARE at a single institution for 2 years were identified from our database. Medical records of the patients were scanned to collect clinicopathological and biochemical results. Patients with previous TARE treatment, patients with previous abnormal biochemical tests and patients with a follow-up of less than 6 months were excluded from the study. Twenty-seven patients (18 male, 9 female; mean age: 61.5±10.5 years, range: 40-77 years) with available pre-treatment and 3 months follow-up biochemical tests were included in the current study. The study population included 10 patients with primary hepatic malignancy (hepatocellular carcinoma) and 17 patients with hepatic metastasis (12 colorectal cancers, two neuroendocrine tumors, one ovarian carcinoma, one breast cancer and one malignant melanoma).

Neutrophil count (normal range: 34-71.1 x10^9/L), C-reactive protein (CRP) (normal range: 0-5 mg/L), aspartate aminotransferase (AST) (normal range: 0-35 IU/L), alanine aminotransferase (ALT) (normal range: 0-35 IU/L), albumin (normal range: 3.5-5.2 g/dL), total bilirubin (normal range: 0.3-1.2 mg/dL), direct bilirubin (normal range: 0-0.2 mg/dL), tumor markers such as alpha-fetoprotein (normal range: 0-9 µg/L), carcinoembryonic antigen (normal range: 0-3 U/mL), Ca-15-3 (normal range: 0-31.3 U/mL) and Ca-125 (normal range: 0-35 U/mL) were measured before the day of treatment. On the 10th day of follow-up, neutrophil count, CRP, AST, ALT, albumin, total and direct bilirubin levels were noted. At the 3rd month of the treatment, all parameters evaluated during pretreatment tests were re-recorded.İstanbul Training and Research Hospital, Clinical Research Ethics Committee (decision no: 1584, date: 21.12.2018).

Technical Information

Before treatment, baseline F-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) imaging (Figure 1) and magnetic resonance imaging were performed. Also, all patients underwent liver angiography with technetium-99m (Tc-99m)-labeled micro-aggregated albumin (MAA) scintigraphy to determine aberrant vasculature and also to calculate the percentage of pulmonary shunting (17). The total volume of the liver and the tumor area were determined using Tc-99m MAA single PET/CT scan (4). Whole liver dose, tumor dose and healthy injected liver dose were all calculated by using the medical internal radiation dose formula (8,18). For both Tc-99m MAA scintigraphy and also for TARE treatment, the femoral artery route was preferred to reach the right and/or left hepatic artery. The patients were discharged home on the following day of the treatment and were seen every 10 days for one month and then regularly every month to monitor side

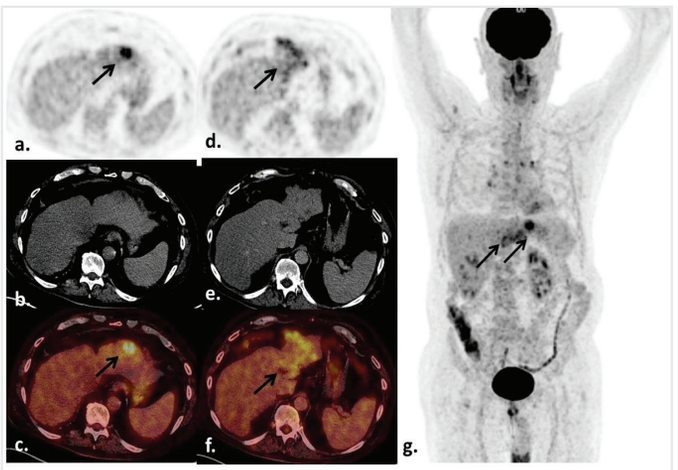

Figure 1. Pretreatment F-18 FDG PET/CT images of a 57-year-old male patient with hepatocellular carcinoma showed high FDG uptake in the left lobe of the liver extending along the portal vein without any distant metastasis: Axial PET (a), CT (b), fusion (c) and MIP images (d) (arrows)

FDG: fluorodeoxyglucose, PET: positron emission tomography, CT: computed tomography, MIP: maximum intensity projection

effects, complications, disease burden, and also for further treatment requirements (4).

Statistical Analysis

All statistical analyses were performed using SPSS software (Version 20.0; SPSS Inc., New York, NY) with a value of $p<0.05$ considered to be statistically significant. Paired t-test was used to compare pretreatment and 10th day early post-treatment and also 3rd month post-treatment biochemical parameters.

Results

Between August 2016 and September 2018, 106 TARE procedures were performed in our institution. A total of 27 TARE procedures in 27 patients, who met the inclusion criteria, were included in the current study. Table 1 lists the descriptive analysis of the biochemical tests just before the treatment, on the 10th day of follow-up and at 3 months of the follow up.

The patient population was heterogeneous with different previous treatment histories including chemotherapy. The majority of patients received treatment to the right lobe (n=22; 81.5%) and 18.5% received treatment only to the left lobe (n=5). The most common side effect following treatment was post-embolization syndrome with fatigue, nausea, low-grade fever, and right upper quadrant pain. No grade 2 or 3 adverse events were detected during follow-up visits in the study population. None of the patients were treated with a total bilirubin level greater than 2 mg/dL or albumin level <3 g/dL.

Statistical significance was observed only between pre-treatment albumin (albumin 1) and 10th day albumin (albumin 2), and between pre-treatment albumin (albumin 1) and 3rd month albumin (albumin 3) levels ($p<0.05$). There was no statistically significant difference between the other biochemical parameters ($p>0.05$) (Table 2).

Table 1. Descriptive analysis of biochemical parameters before and early or late after treatment

Variable	Mean ± SD	Range
Pre-treatment parameters		
Neutrophil-1 (n=27)	4.6±2.1	1.2-10.5
CRP-1 (n=27)	4.1±4.9	0.2-14.2
ALT-1 (n=27)	32.5±26.9	11-124
AST-1 (n=27)	44.5±32.2	14-166
Albumin-1 (n=27)	4.0±0.5	3.3-5.9
Total bilirubin-1 (n=27)	0.9±0.45	0.35-1.89
Direct bilirubin-1 (n=27)	0.2±0. 2	0.05-1.01
AFP-1 (n=10)	7315.9±17225.5	1.3-54000
CEA-1 (n=12)	26.2±23.6	3.6-72.4
Ca-15-3.1 (n=1)	76.2	-
Ca-125.1 (n=2)	44.3±22.8	26.0-59.0
Post-treatment (Early) Parameters (10th day)		
Neutrophil-2	4.3±1.7	1.7-8.7
CRP-2	9.7±12.9	0.7-49.2
ALT-2	41.5±29.2	9-116
AST-2	58.1±33.1	17-141
Albumin-2	3.7±0.5	2.3-4.4
Total bilirubin-2	1.4±2.7	0.4-14.4
Direct bilirubin-2	0.5±1.5	0.03-7.6
Post-treatment (late) parameters (3rd month)		
Neutrophil-3	5.04±3.1	2.5-16.3
CRP-3	10.8±17.9	0.5-67.2
ALT-3	39.0±33.9	11-171
AST-3	55.0±55.8	28.0-300.0
Albumin-3	3.5±0.6	2.5-4.8
Total bilirubin-3	1.8±3.2	0.5-17.05
Direct bilirubin-3	0.7±1.8	0.04-9.35
AFP-3	16938.9±44706.9	2.06-142760.0
CEA-3	25.7±38.6	1.4-96.1
Ca-15-3.3	118.1	-
Ca-125.1 (n=2)	111.5±117.2	28.6-194.4

SD: standard deviation, CRP: C-reactive protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, AFP: alpha-fetoprotein, CEA: carcinoembryonic antigen

Discussion

Our institutional experience of TARE with Y-90 microsphere has shown that it is a relatively safe local treatment option for unresectable intrahepatic malignancies in the scope of biochemical parameters, although albumin levels changed significantly early after the treatment and in the late follow up.

TARE can selectively provide very high radiation exposure to tumor tissue with fewer side effects. Previous studies have shown that this therapy is an effective and safe option for unresectable liver malignancies such

Table 2. Statistical analysis of biochemical parameters before treatment, early or late after treatment

Biochemical parameters	p
ALT-1/ALT-2	0.174
ALT-1/ALT-3	0.402
AST-1/AST-2	0.059
AST-1/AST-3	0.145
Neutrophil-1/Neutrophil-2	0.528
Neutrophil-1/Neutrophil-3	0.540
CRP-1/CRP-2	0.081
CRP-1/CRP-3	0.122
Total Bilirubin-1/Total bilirubin-2	0.299
Total Bilirubin-1/Total bilirubin-3	0.162
Direct Bilirubin-1/Direct bilirubin-2	0.278
Direct Bilirubin-1/Direct bilirubin-3	0.170
Albumin-1/Albumin-2	0.001
Albumin-1/Albumin-3	0.001
AFP-1/AFP-3	0.320
CEA-1/CEA-3	0.875

p value<0.05=statistically significant

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, AFP: alpha-fetoprotein, CEA: carcinoembryonic antigen

as hepatocellular carcinoma and liver metastases from colorectal and breast cancer, neuroendocrine tumors, melanoma, pancreatic, renal and lung cancer (6,10,14,19).

Y-90 is a high-energy beta emitter that is used to label microspheres. Radiolabeled microspheres cannot get through venous capillaries due to their larger diameter than the end arterial capillary bed. So, Y-90 labeled microspheres are trapped in the tumor bed and high radiation doses can be achieved in the tumor tissue, causing irreversible cell damage in the epithelial, stromal, and endothelial cells of the area (14). Endothelial cells were suggested to be the main and first target of internal radiation therapy. Endothelial cells of tumors are damaged and cell death is observed afterwards (20,21). In addition, malfunction and transient failure of the liver may be observed after treatment, which may lead to insufficient production of some proteins (22). These mechanisms may explain why albumin levels in this study were significantly decreased during very early and late follow-up.

Common side effects of treatment are nausea, vomiting, mild abdominal pain and fever with a reported incidence of 20-70%, and may be associated with systemic reaction to endothelial damage (14,23). Vascular dissection/occlusions, pseudo-aneurysms, liver abscess formation, biliomas, cholecystitis, gastritis, duodenitis, pleural effusions and perihepatic fluid collections are some of the mild to serious complications after TARE (6). Transaminase enzymes may increase transiently in the first 4-6 weeks of treatment and may last up to 2-3 months (14). It has been shown that liver toxicity is up to 96% in terms of transaminase levels in patients treated with the whole liver approach (24). In another phase 2 study, altered bilirubin levels were reported at 3 months in 13.5% of patients (25). In contrast, no clinically apparent hepatic toxicity was observed in another large cohort study (26). In the current study, similar to the results of the last study, we could not demonstrate significant fluctuation of transaminases or bilirubin levels either in the early or late follow-up of patients.

Radiation-induced liver damage was described many years ago in the scope of external beam radiotherapy that is related with centrilobular vein damage (27). In this syndrome, ascites without jaundice, elevated alkaline phosphatase and less frequently increased liver transaminases are observed (28). On the other hand, radioembolization-induced liver damage, which is a typical liver toxicity syndrome specifically associated with radioembolization, has recently been described (29). Severe abdominal pain, ascites, jaundice, bilirubin elevation, variable elevation of gamma gamma glutamyl transferase, and alkaline phosphatase without significant increase in transaminase enzymes and decreasing blood albumin levels usually at the 3rd month of treatment are the components of the syndrome (14,28). This can also promote our study data that albumin is the critical parameter that must be checked regularly. In a recently published study, it was shown that significant decline in overall survival was observed as serum albumin, and hence hepatic synthetic function, even with the majority of patients having a normal total bilirubin. They also concluded that the median overall survival of patients with normal serum albumin was greater and that patients with an albumin below 3 g/dL might not derive a significant clinical benefit from treatment with Y-90 TARE when albumin fell below 3 g/dL (4). Similarly, an albumin level >3 g/dL has been previously reported as a predictor of survival in a group of patients with colorectal histology treated with Y-90 TARE (30).

The primary purpose of this study was to identify the effect of treatment on early and late follow-up biochemical parameters that could be used to predict safety and efficacy.

Study Limitations

Our study population was heterogeneous in terms of demographics and histology, which is one of the main limitations along with retrospective design. Additionally, follow-up duration was not long enough to give information about relationship between survival and biochemical parameters.

Conclusion

Our experience with Y-90 TARE has shown that it is a relatively safe treatment option in the scope of biochemical parameters for properly screened patients with intrahepatic malignancies. Our data suggests that the critical biochemical parameter is albumin, which should be checked regularly before, early and late after treatment.

Ethics Committee Approval: İstanbul Training and Research Hospital, Clinical Research Ethics Committee (decision no: 1584, date: 21.12.2018).

Informed Consent: Informed consent forms were obtained.

Peer-review: Internally peer-reviewed.

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