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TRANSARTERIAL CHEMOEMBOLIZATION AND EARLY ARTERIAL COMPLICATIONS AFTER LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

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Objective: to evaluate the possible influence of neoadjuvant transarterial chemoembolization (TACE) on development of early arterial complications after orthotopic liver transplantation (OLTx). **Materials and methods.** The work is based on treatment-related data of 250 recipients. The analyzed group included 21 patients with hepatocellular carcinoma (HCC). In all recipients who underwent primary transplantation (n = 228), possible negative factors influencing the development of early arterial complications were analyzed, such as degree of allograft steatosis, cold and warm ischemia time, revascularization duration, blood pressure level after arterial reconstruction, and exchange transfusion volume. **Results.** The degree of allograft steatosis did not differ between HCC patients and the general sample (95% CI, p = 0.25). No early arterial complications were revealed during TACE. There was no significant difference in preservation parameters, arterial revascularization time, systolic blood pressure level at blood flow start, and exchange transfusion volume (CI 95%, p > 0.05). The incidence of early vascular complications in the study group was 16.7%, it did not differ from the entire sample (95% CI, p = 0.96). **Conclusion.** The incidence of early arterial complications of OLTx in patients who underwent TACE does not significantly increase both according to the literature and our own findings. When vascular complications of OLTx occur, image-guided endovascular intervention is the method of choice for treatment.

Keywords: liver transplantation, neoadjuvant chemoembolization, early arterial complications.

INTRODUCTION

TACE is a recognized palliative treatment for HCC. In patients with HCC and cirrhotic transformation of the organ before a scheduled transplantation, neoadjuvant TACE reduces tumor size, biological activity of tumor and prolongs the waiting list time without significant progression. The literature describes specific arterial complications of embolization – intimal detachment, stenosis and thrombosis, leading to a shortage in blood supply to the organ, development of early complications, including in patients with subsequent liver transplantation [2, 3, 5].

MATERIALS AND METHODS

The work is based on the data of 250 recipients. The analyzed group included 21 patients with HCC, 9 men and 12 women aged 27.9 to 64.6 years (mean age was 49.7 ± 7.48). In absolute majority, HCC resulted from chronic viral hepatitis and cirrhosis. To assess the impact of neoadjuvant TACE on early arterial complications in all primary transplant recipients (total group, n = 228), possible adverse events were analyzed. In recipients on the waiting list who underwent TACE, these were intimal dissection and aneurysm, impaired arterial perfusion of the organ, and arterial thrombosis during arterial hepatography. Eighteen recipients underwent 1 to 7 courses of neoadjuvant TACE, including four cases that combined pre-transplant liver resection. In two cases, radiofrequency ablation and liver resection without TACE were done.

Only one patient did not receive neoadjuvant therapy.

Before neoadjuvant TACE, 7 of 21 potential candidates for OLTx did not meet the Milan criteria.

After arterial hepatography and reverse portography, embolizumab, a suspension of oil contrast (lipiodol 4 to 10 mL) and antitumor drugs (doxorubicin 40–60 mg, mitomycin 10–15 mg) or 70 mg doxorubicin in saturable spheres, was injected superselectively into vessels feeding the tumor (DEB, patients 4, 8, and 9). The procedure may have been supplemented by mechanical occlusion of the hepatic artery branches feeding the tumor with a fine-cut hemostatic sponge. There were no immediate complications of the procedure. Length of stay in the hospital for TACE ranged from 3 to 9 days (5 days on average). Subsequent liver transplantation after neoadjuvant treatment was performed within 2 days to 10 months.

In all cases, cold perfusion during allograft preparation was performed with custodiol solution (HTK "Custodiol", Kohler, Germany) in 8–14 liters. Subsequently, during liver transplantation, we recorded the preservation parameters – cold and warm ischemia

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time; arterial revascularization duration; blood pressure after arterial reconstruction. A physical intraoperative assessment was carried out – the presence of pulsatile flow distal to the formed anastomosis, volumetric flow rate was determined by Doppler ultrasound flowmetry. An at least 100 mL/min volumetric flow rate was considered adequate. Exchange transfusion volume was determined by mathematical addition of transfused donor and collected autoerythrocyte masses using a cell saver machine. The period between the last TACE and organ transplant surgery was also evaluated. Outcomes of repeated transplants (n = 22) were excluded from the study.

RESULTS

In the sex and age distribution, HCC patients who underwent neoadjuvant TACE did not differ significantly from other recipients ($p > 0.05$ in both samples). The level of macrovesicular steatosis of the allograft prepared for transplantation did not differ between the HCC patient groups and the overall sample (95% CI, $p = 0.25$). Among the seven patients who did not initially meet the Milan criteria, neoadjuvant TACE was performed in six cases, which in half of the cases reduced the tumor size to the above criteria. There was a significant decrease in the median levels of alpha-fetoprotein before and after comprehensive neoadjuvant treatment – from 86 to 23.6 IU/mL ($p < 0.05$).

There were no deaths from early arterial complications of OLTx in the study group. There were also no angiographic complications – intimal injury, reduced hepatic arterial perfusion during a postponed study, and hepatic artery thrombosis in waitlisted patients.

Average cold ischemia time in the analyzed group was 377.2 minutes, whereas the overall time for all transplants was 397.8 minutes; warm ischemia time was 54 and 47.8 minutes, respectively ($P > 0.05$). At arterial blood flow start, there was systolic blood pressure below 100 mm Hg in 41.7% of 228 recipients, and in 33.3% of the analyzed group. No significant difference affecting the development of early complications (95% CI, $p = 0.49$) were found. Exchange transfusion volume was comparable in all patients and those who underwent neoadjuvant treatment (Table 2).

Three patients in the study group (16.7%) had early vascular complications. In one case, blood supply deficiency was corrected intraoperatively by forming an anastomosis with the aorta (patient #16). In a combination of hepatic artery stenosis of the graft and steal syndrome (patient #14), a successful balloon angioplasty of arterial anastomosis and splenic embolization were performed four days later; in one patient, the steal syndrome was eliminated by splenic embolization on day 6 after OLTx (patient #18).

We should note a case of late hepatic arterial thrombosis with the development of necrotizing cholangitis, which was observed at day 32 and was not related to the TACE procedure and OLTx technique (patient #6).

Table 1

Neoadjuvant therapy options for patients on the waiting list

S/N	Patient, age in years	Diagnosis, stage	Secondary diagnosis	Previous treatment
1	K., 27	HCC T4N0M0		4 TACE
2	U., 48	HCC T3N0M0	PBC	1 TACE
3	K., 49	HCC T3N0M0	CHBI	2 TACE
4	K., 43	HCC T2N0M0	CHBI	1 TACE (DEB)
5	E., 49	HCC T3N0M0	CHCI	3 TACE
6	K., 53	HCC T2N0M0	CHBI	4 TACE, open radiofrequency ablation
7	S., 60	HCC T2N0M0	CHCI	2 TACE
8	R., 44	HCC T1N0M0	CHBI	1 TACE (DEB)
9	Z., 54	HCC T3N0M0	CHCI	2 TACE (DEB)
10	K., 52	HCC T2N0M0	CHCI	7 TACE
11	B., 58	HCC T3N0M0	CHCI	2 TACE, video laparoscopic resection, Radiofrequency ablation
12	N., 54	HCC T2N0M0	CHCI	5 TACE
13	T., 44	HCC T2N0M0	CHCI	2 TACE
14	S., 47	HCC T2N0M0	CHCI	2 TACE/TIPS
15	P., 52	HCC T3N0M0	CHCI	6 TACE, video laparoscopic resection
16	S., 64	HCC T3N0M0	PBC	2 TACE, video laparoscopic resection
17	P., 42	HCC T2N0M0	CHCI	None
18	P., 53	HCC T2N0M0	CHCI	2 TACE
19	R., 46	HCC T1N0M0	CHCI	Radiofrequency ablation
20	S., 46	HCC T3N0M0	CHBI	Video laparoscopic resection
21	K., 44	HCC T2N0M0	CHCI	1 TACE

Thus, in the early post-OLTx period, incidence of vascular complications was 16.2% in all patients and 16.7% in recipients who received neoadjuvant TACE. There was no significant difference (95% CI, p = 0.96).

One-year graft survival (Kaplan–Maier estimates) was 91% (Fig.).

DISCUSSION

Arterial and subsequent biliary complications are the main cause of graft dysfunction and patient death after OLTx. The severity of early vascular complications after liver transplantation is incomparable with the general surgical problems of the early postoperative period. Hepatic artery thrombosis leads to severe graft dysfunction and loss, which explains the high mortality rates. Arterial stenosis and arterial kink, and steal syndrome are the cause of arterial insufficiency in a transplanted organ, they determine the subsequent formation of multiple biliary strictures, deterioration of its function and recipient's condition, which eventually requires retransplantation in 20–40% of cases [9, 3].

Today, TACE is regarded as the standard of care for patients with HCC against a background of cirrhosis. It allows to achieve "a decrease in the stage of the disease". It supports the status of their stay on the waiting list, including the Milan criteria [4]. Our experience shows superselective TACE allows 60% of potential candidates to prolong their stay on the waiting list for one year without significant progression [6, 8].

Severe complications of TACE in the form of intimal dissection and acute hepatic artery thrombosis usually occur when performing lobular embolization and with little experience in such procedures. Our research center performs several hundred chemoembolizations in patients with malignant liver tumors annually. Mortality is less than 2%, and the side effects do not require surgical intervention [7].

Current literature discusses the possible relationship of early vascular complications of OLTx in patients after neoadjuvant TACE. For example, D. Sneiders et al. analyzed the outcomes of OLTx after TACE in 1,122 patients in 14 retrospective studies. Both vascular and biliary complications of OLTx were studied. All patients only after TACE with doxorubicin were included, but the technique itself was not considered: the authors in this meta-analysis did not separate classical oil TACE and DEB; they allowed lobular embolization in multiple sources of blood supply. There was increased incidence

Table 2

Comparative indicators and differences by groups

Parameters (mean values)	General group (n = 228)	Analyzed group (n = 18)	P
Cold ischemia, minutes	397.8	377.2	>0.05
Warm ischemia, minutes	47.8	54	>0.05
Arterial revascularization, minutes	48.3	56	>0.05
BP level at the time of arterial start, <100 mm Hg/%	41.7	33.3	<0.5
Exchange transfusion volume, mL	1520	1572.8	>0.05

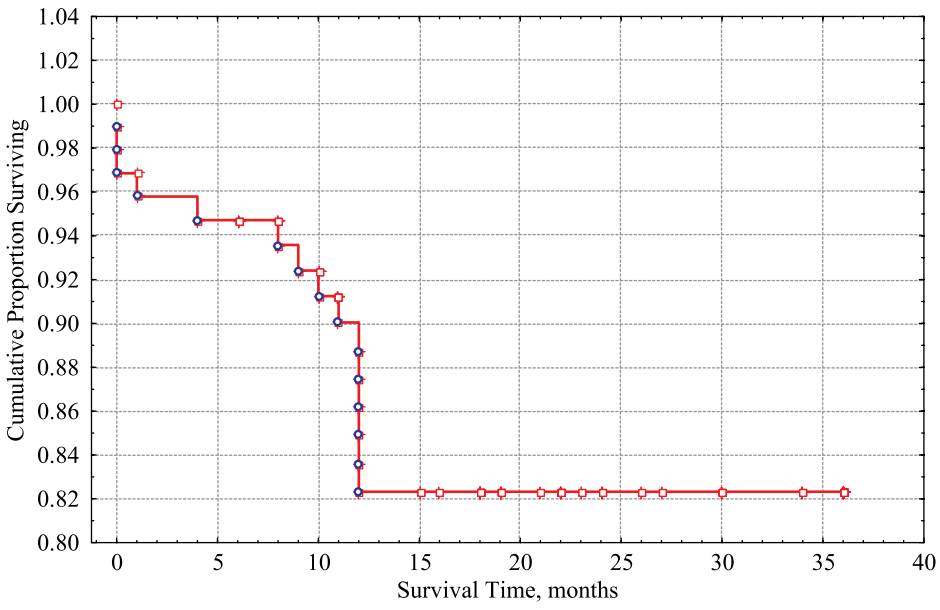

Fig. Cumulative graft survival (Kaplan–Maier)

of vascular complications of OLTx after TACE, but none of them were significant (p = 0.02) [3]. At the same time, achievement of TACE effect in patients with advanced HCC against the background of cirrhosis is a "bridge" to OLTx. Their survival is comparable to that of recipients who meet the Milan criteria; in addition, TACE potentially reduces the risk of relapse and progression [3, 5, 8].

A number of publications have studied histological changes in the wall of the lobar hepatic arteries of the explant. Panaro F. et al. detected arterial wall edema, fibrosis and hemorrhagic intimal necrosis in 12 of 32 patients with neoadjuvant TACE. However, there was no significant difference in the number of vascular complications of OLTx (28% each in the TACE group and control group) and mortality from graft loss (6.25% vs 5.75%) (p = 0.01) [4].

At our research center, TACE in HCC patients on the OLTx waiting list is performed using microcatheter technique only, always superselectively by definition. After performing 49 TACE procedures in 18 patients from the OLTx waiting list at our center, no consequences were noted [6, 8]. The incidence of vascular complications of transplantation was not significant – 16.2% in all patients and 16.7% in recipients who received neoadjuvant TACE (p = 0.96).

CONCLUSION

The incidence of early arterial complications of OLTx in TACE recipients, according to literature and in our observations, has not increased.

Achieving the effect of the ongoing neoadjuvant treatment in patients with advanced stages of HCC against a background of cirrhosis is a "bridge" to OLTx. Patient survival is comparable to that of recipients who met the Milan criteria.

In the case of vascular complications of OLTx, the treatment method of choice is X-ray image-guided endovascular interventions.

The authors declare no conflict of interest.

REFERENCES

1. *Li H, Li B, Wei Y, Yan L, Wen T, Wang W et al.* Preoperative transarterial chemoembolization does not increase hepatic artery complications after liver transplantation: A single center 12-year experience. *Clin Res Hepatol Gastroenterol*. 2015 Sep; 39 (4): 451–457.
2. *Gilbo N, Van Praet L, Jochmans I, Sainz-Barriga M, Verslype C, Maleux G et al*. Pre-operative trans-catheter arterial chemo-embolization increases hepatic artery thrombosis after liver transplantation – a retrospective study. *Transpl Int*. 2018 Jan; 31 (1): 71–81.
3. *Sneiders D, Houwen T, Pengel LHM, Polak WG, Dor FJMF, Hartog H.* Systematic Review and Meta-Analysis of Posttransplant Hepatic Artery and Biliary Complications in Patients Treated With Transarterial Chemoembolization Before Liver Transplantation. *Transplantation*. 2018 Jan; 102 (1): 88–96.
4. *Ogawa K, Takada Y.* Role of Pretransplant Treatments for Patients with Hepatocellular Carcinoma Waiting for Liver Transplantation. *Cancers (Basel)*. 2022 Jan 13; 14 (2): 396.
5. *Panaro F, Ramos J, Gallix B, Mercier G, Herrero A, Niampa H et al*. Hepatic artery complications following liver transplantation. Does preoperative chemoembolization impact the postoperative course? *HAL*. Id: hal-03562828. https://hal.archives-ouvertes.fr/hal-03562828. Submitted on 9 Feb 2022.
6. *Polekhin A.S., Tarazov P.G., Polikarpov A.A., Granov D.A.* Transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma on advanced liver cirrhosis. *Grekov's Bulletin of Surgery*. 2019; 178 (6): 29–35.
7. *Polikarpov AA*. Rentgenoendovaskulyarnye vmeshatel'stva v lechenii nerezektabel'nykh zlokachestvennykh opukholey pecheni: avtoref. dis. … d-ra med. nauk. Sankt-Peterburg, 2006. 42 s.
8. *Granov DA, Polekhin AS, Tarazov PG, Rutkin IO, Tileubergenov II, Borovik VV*. Transcatheter hepatic arterial chemoembolization in cirrhotic patients with hepatocellular carcinoma before liver transplantation: the prognostic value of alpha-fetoprotein concentrations. *Russian Journal of Transplantology and Artificial Organs*. 2020; 22 (4): 52–57.
9. *Moiseenko AV, Polikarpov AA, Tarazov PG, Tileubergenov II, Maystrenko DN, Granov DA*. Endovascular interventions in correction of arterial complications after orthotopic liver transplantation. *Journal Diagnostic & interventional radiology*. 2021; 15 (1): 51–58.

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