Transarterial Chemoembolization (TACE) with Lipiodol® in HCC Patients

Technical, clinical and imagistic aspects

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Hepatocellurar carcinoma (HCC) is the most frequent primary hepatic tumor, the vast majority of patients have less than a 12 month survival rate. The aim of this study was to evaluate the efficacy of TACE in patients with HCC, based on a case series and literature review. The study included 12 consecutive patients with HCC who underwent surgical treatment (resection, liver transplantation ± resection) at the Department of Transplantation and Surgery, Semmelweis University, Budapest, during 2009-2015. All the patients received at least one TACE session. Patients with BCLC B-stage who benefit from TACE and another alternative therapy (eg, RFA) may be associated with or exhibit tumor stagnation, or tumor necrosis in most cases. In C BCLC stages, desperate cases - the two patients to whom TACE was the last therapeutic attitude, despite the predicted prognosis, TACE assured the prolongation of life and increased life quality. In the majority of patients in this study, stage A BCLC, chemoembolization was a therapeutic attitude that allowed subsequent liver transplantation (when it was not feasible initially due to tumor size) or liver resection in apparently inoperable cases. The arterial chemotherapy is the unanimously accepted indication in patients with stage B, BCLC. The data presented encourages us to opt for TACE with the intention of destaging BCLC and giving an operability character to the hepatic tumors (resection ± hepatic transplantation). In stage C BCLC, TACE can be a last attempt to improve the quality of life and to control tumor progression.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, liver transplantation, liver resection

Hepatocellular carcinoma (HCC) is the most frequently encountered primary hepatic tumor[1], depending on geographic area [2]. It represents 80%-90% of all primary hepatic tumors[2]. In most of the cases, HCC is diagnosed in late stages. Despite individualized treatment, the majority of patients have a survival rate of less than 12 months [3-5]. In the year 2015, at a global level, HCC was the 4th cause of cancer-reated death and the 6th most frequently encountered form of cancer. According to the *Global Burden of Disease Liver Cancer Collaboration*, the incidence of HCC has grown 75% from 1990 until 2015 when it reached almost 900,000 new cases per year, registering almost 850,000 deaths [6,7].

The indications of radical, pure surgical therapies have certain limitations. For exemple, liver resection is feasible only for 15-30% of the patients and liver transplantation is limited by strict criteria (most of the times, HCC condition is discovered in stages beyond Milan criteria) [8-10]. This was the context of developing palliative techniques, such as: transarterial chemoembolisation(TACE), radio-frequency ablation(RFA), percutaneous ethanol injection(PEI), locoregional therapies, etc. The alternative therapies are a result of the need for downstaging HCC and bridging to curative treatment [11,12].

Trans arterial chemoembolization (TACE) was used for the first time in Japan in January 1981 through the administration of a mixture made up of an antitumor agent (neocarzinostatin) and Lipiodol [13].

Synthesized in 1901 by the French chemist Marcel Guerbet, Lipiodol, an ethiodized oil injection, is a sterile injectable radio-opaque agent. Each milliliter contains 480 mg of iodine organically combined with ethyl esters of fatty acids of poopy seed oil [14].

The last 30 years have imposed the most widely used technology with TACE, the mixture of Lipiodol with a chemotherapeutic drug (doxorubicin or cisplatin) later realizing arterial sealing through the administration of a substance with embolic properties [15,16].

The aim of this study was to evaluate the efficacy of TACE in patients with HCC, based on a case series and literature review.

Experimental part

The study included 12 consecutive patients with HCC (table 1) who underwent surgical treatment (resection, OLTx ± resection) at the Department of Transplantation and Surgery, Semmelweis University, Budapest, during 2009-2015. All the patients received at least one TACE session. The agreement of the local Ethical Comitee was obtained for retrospective evaluation of the cases.

Half of the patients (n=6) were diagnosed with one tumor and other 4 displayed multiple non-small tumors (tumors located in two segments of the same division). The rest of the patients (n=2) presented multiple bilobar tumors, one patient exhibited two tumors located in two different anatomical segments, and another one presented disseminated tumors in the hepatic parenchyma with

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Total Number of Patients	12 Patients
Men	7 Patients
Women	5 Patients
Median Age	62,33 years
Minimum Age	58 years
Maximum Age	73 years
Unique Tumors	6 Patients
Multiple Tumors	6 Patients

Table 1
CLINICOPATHOLOGICAL PARAMETERS

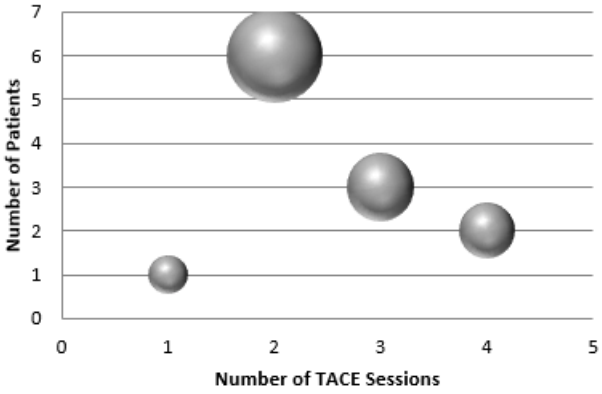

Fig. 1. The number of TACE sessions per patient

infiltration of 4 segments (table 1). The median diameter of the tumor was 33.9 mm (range between 12 and 70 mm).

In all cases, HCC was developed on the cirrhosis background. It was related on infection with HCV (n=6), HBV (n=1), or combined HBV+HCV infection (n=1). Alcoholic (n=1) and cryptogenic cirrhosis (n=3) was also identified.

To perform TACE, the left brachial artery was used for catheter insertion. When this access point was not feasible, we performed puncture and catheterization of the femoral artery. Initially, we advanced with a 4-5 French microcatheter and imagistically identified the tumor and the segmental artery. After visualizing the arterial source of the tumor, we introduced through the original catheter a thinner one (2-2,9 French). This insertion aimed to realize a superselective embolization. This type of catheterization and TACE was used in according to the previous data published in literature, being the technique with low rate of associated systemic complications [15-18].

We used, as chemotherapeutic agent, 50-75 mg/m^2 Doxorubicin. The dose was adapted based on the tumor size and the total serum bilirubin vales, according to the European Association of Studies of the Liver recommendations [19-22]. The used dose was: 25 mg/m^2 in patients with 51.3-85.5 µmol/L of bilirubin, 50 mg/m^2 for 25.6–51.3 µmol/L, and 75 mg/m^2 , for patients with bilirubinemia <25.6 µmol/L

Based on the European Guide recommendations, a minimum interval of 2-6 months between two consecutive sessions of TACE was respected [21, 22]. The patients have benefited from a maximum of 4 sessions of TACE, in a period of 18 (2 patients), or 12 months (6 patients). The average number of sessions of TACE was 2.5 per patient (fig. 1).

Results and discussions

HCC is more frequent in males, with a M:F ratio of 2-3:1. The discrepancy in gender distribution is not as significant in Latin America and South America, but in Western European countries there is a difference of up to 5 times of the HCC between males and females [17]. In our material, TACE was considered as the first line therapy (n=9) or was performed in patients with postoperative recurrence (n=3). In one of the three patients, RFA was firstly done and TACE was the second choice. For the majority of patients (n=10), TACE induced HCC downstaging. In two of the patients, aggressive relapse was seen and, despite TACE, the average survival rate was 4.5 months only (table 2). Ortotopic liver transplantation was applied in 6 patients, with an average waiting interval of 4.16 months (range 1 to 8 months).

	Number of Patients	Minimum Interval Period	Maximum Interval Period	Average Interval Period
TACE → OLTx	6	1 month	8 months	4,16 months
TACE → RFA	2	6 months	44 months	25 months
TACE → Resection	2	2 months	18 months	10 months
TACE Last therapeutic Approach		Minimum Survival	Maximum Survival	Average Survival
TACE → death	2	1 month	8 months	4,5 months

Table 2
THE TIME INTERVAL BETWEEN TACE

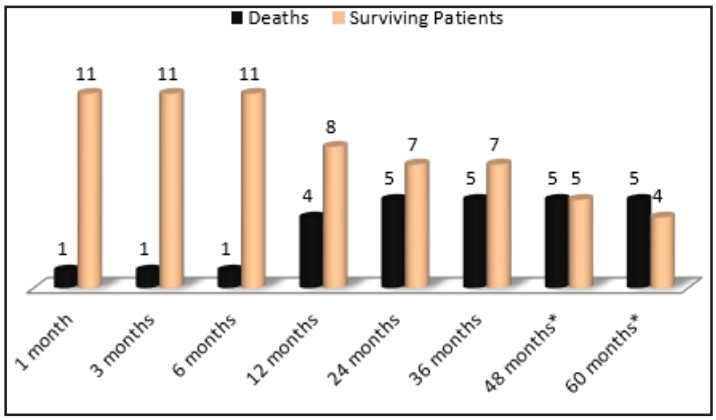

Fig. 2 Number of deaths according to the last session of chemoembolization

** for 3 patients, the last chemoembolisation session was done earlier than 48 months from the beginning of this study.*

Hepatic resection was feasible for the rest of the patients (n=4). Two of these patients needed RFA/RFA + tumor alcoholization in the interval of time between TACE and resection (table 2).

Systemic complications-related death occurred in one of the 12 patients, one month after TACE. No deaths were registered at 3 or 6 months post-TACE. Three patients died 12 months after the last session of TACE (fig. 2).

Compared with the previous TACE CT examination, there appeared two satellite tumors with a maximum diameter of 12 mm and viable tumor tissue of 12 mm thickness circumferentially to the existing tumor (the tumor with imaging signs of necrosis), with the aspect of a tumoral halo (table 3).

Following chemoembolization, there was a decrease in tumor diameter, resulting in an average size of 32.63 mm post TACE, compared with 33.9 mm before TACE. Despite the numerous existing guidelines and differences in the therapeutic approach of HCC for the European Society for the Study of Liver (EASL), and the American Society for the Study of Liver Disease (AASLD), etc., the last decade imposed the staging system of cancer liver Barcelona (BCLC) [23-25].

According to BCLC, the gold standard in the treatment of intermediate HCC - stage B is TACE transcritical chemoembolization [24,26]. The data from our study is superposable with the EASL, AASLD recommendations [21,22]. Patients with BCLC B-stage who benefit from TACE and another alternative therapy (eg, RFA) may be associated with or exhibit tumor stagnation, or tumor necrosis in most cases [26]. In C stages BCLC, desperate cases - the two patients to whom TACE was the last therapeutic attitude, despite the predicted prognosis, TACE assured the prolongation of life and increased life quality [27-29]. In the majority of patients in this study, stage A BCLC, chemoembolization was a therapeutic attitude that allowed subsequent liver transplantation (when it was not

Table 3

TUMOR DIAMETER ACCORDING TO HCC LOCALIZATION, BEFORE(BLACK COLOUR) AND AFTER(RED COLOUR)TACE

Patients	1	2	3	4	5	6	7	8	9	10	11	12
Segment 1	-	-	-	-	-	-	-	-	-	-	-	-
Segment 2	-	-	30 20†/12'	-	-	-	-	-	60 60†	-	12 15	68 65†
Segment 3	-	-	-	-	-	-	30 35	-	-	-	18 25	32 40
Segment 4	-	30 25	-	-	-	-	70 63†	-	-	33 30†	-	-
Segment 5	-	-	-	-	-	20 20†	-	-	-	-	-	-
Segment 6	25 30/12*	40 30†	-	-	40 45†	-	-	-	-	-	20 30	-
Segment 7	-	-	-	-	-	-	-	-	-	-	-	-
Segment 8	40 40†	-	-	45 40†	- 12*	20 20†	-	30 29†	-	-	15 20	-

** new tumoral tissue in comparison to the previous examination before TACE*

' viable tumoral tissue localized circumferential to the area of tumoral necrosis ,"tumoral halo" aspect

† CT signs that suggest tumoral necrosis

Minimum tumor dimension*	12 mm
Maximum tumor dimension*	70 mm
Average tumor dimension*	33.9 mm
Minimum tumor dimension¨	12 mm
Maximum tumor dimension¨	65 mm
Average tumor dimension¨	32.63 mm

Table 4

EFFICACY OF CHEMOEMBOLIZATION DEMONSTRATED IMAGISTICALLY BY TUMOR VOLUME REDUCTION

**CT pre TACE*

¨ CT post TACE

feasible initially due to tumor size) or liver resection in apparently inoperable cases [30-33].

Conclusions

TACE is a feasible technique which assures downstaging of HCC, bridging to curative treatment and a notable way of increasing life quality for patients.

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