Trans-arterial chemoembolization (TACE) in treatment of non-resectable hepatocellular carcinoma: comparative study between conventional TACE and drug eluting bead TACE

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ABSTRACT
To compare tumour response and complications of conventional TACE with lipidol versus DEB-TACE in the treatment of non-resectable HCC. Prospective non randomized comparative clinical trial was performed for patients receiving TACE at interventional radiology unit in Radiodiagnosis department in Zagazig university hospitals. Forty patients were included in this study, 16 patients were treated with drug eluting beads TACE and 24 patients were treated with conventional TACE. Follow up triphasic CT was performed 1 month after the procedure, we found that complete response was 6 cases (25%) in c TACE group, and 4 cases (25%) in drug eluting bead TACE group, Partial response was achieved in 11 cases (45.8%) in c TACE group, and in 8 cases (50%) in DEB-TACE group, Cases with stable disease were 5 cases (20.8%) in c TACE group, and it was 3 cases (18.7%) in DEB-TACE group, progressive disease is noted in two cases (8.3%) in c TACE group, and one case (6.2%) in drug eluting TACE group. Complications were as follow: 18 cases (75%) with abdominal pain in c TACE group, and 6 cases (37.5%) with abdominal pain in DEB-TACE group, Nausea and vomiting were noted in 13 cases (54.17%) in c TACE group and in 3 cases (18.75%) in DEB-TACE group, Alopecia was noted in 8 cases (33.3%) in c TACE group and in one case (6.25%) in DEB-TACE group. There were no significant differences between two groups regarding tumour response after 1 month. Almost all complications were significantly lower in DEB-TACE group than in c TACE group, especially with abdominal pain, nausea, vomiting and alopecia. Abbreviations: c TACE: conventional trans-arterial chemoembolization, DEB TACE: drug eluting beads trans-arterial chemoembolization, HCC: hepatocellular carcinoma, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

INTRODUCTION
Hepatocellular carcinoma (HCC) is a standout amongst the most widely recognized cancers with a yearly rate of around 750000 cases for every year around the world (Jemal et al., 2011). The dominant part of patients are diagnosed at middle of the road or progressed clinical stages, which rejects them from possibly curative treatment, for example, resection, liver transplantation, or local ablation. As indicated by the Barcelona Clinic Liver Cancer
Amgad M. Elsheikh et al., Int. J. Res. Pharm. Sci., 2020, 11(3), 4733-4741

grouping (BCLC), transarterial chemoembolization (TACE) is the standard treatment for patients with intermediate stage HCC (EASL-EORTC, 2012). The great bulk of HCC patients are not candidates for liver resection because they have advanced disease with widespread tumour growth, significantly impaired functional reserve of the cirrhotic liver and/or existing portal hypertension, possibly with associated thrombosis of the portal vein (Llovet et al., 2003). Transarterial chemoembolization (TACE) currently represents the standard treatment for patients with advanced non-resectable HCC (Bruix and Sherman, 2005). In spite of a number of publications, there is still no agreement on the choice of chemotherapeutic agents and on the TACE treatment regime (Llovet et al., 2003). Drug-eluting bead transarterial chemoembolization (DEB-TACE) has been extensively commercially available since 2006. Since then, DEB-TACE has become the de facto standard in a lot of centers worldwide, many investigators believe it to be more beneficial than conventional TACE with lipiodol (cTACE) (Bargellini et al., 2014). Drug-eluting bead is a new drug that enables embolization of vessels supplying hypervascularized malignant tumours with concurrent administration of a local, controlled, sustained dose of a chemotherapeutic agent to the tumour (Lewis et al., 2007). In this clinical trial we compare conventional TACE versus DEB TACE regarding tumour response and complications.

MATERIALS AND METHODS

Study design

The study was approved by our Institutional Review Board. A prospective non randomized comparative clinical trial was performed for patients receiving TACE at interventional radiology unit in Radiodiagnosis Department in Zagazig University Hospitals between January 2018 and December 2019. Complications and tumour response rate were assessed.

Study Population

Through 2 years, selected patients, who attended to Radiodiagnosis Department and met the inclusion criteria for transarterial chemo-embolization of hepatocellular carcinoma were included in the study. Forty patients were included in this study, 16 patients were treated with Drug eluting beads TACE and 24 patients were treated with conventional TACE.

Inclusion criteria

1. Any age group and sex.

2. Patients suffering from hepatocellular carcinoma and are candidate for TACE,

A) Tumor size is usually more than 5 cm.
B) Patients with multinodular tumors without vascular invasion or extrahepatic spread.
C) Patients with early stage HCC when surgical options or percutaneous ablation are contraindicated or not suitable.
D) Liver functional reserve is a critical component for careful patient selection, patients should present with relatively well preserved liver function (mostly Child Pugh A or B without ascites).

Exclusion criteria

1. Patients with complete portal vein thrombosis.
2. Patients with contra-indication to contrast media administration.
3. Patients who are candidate for radio-frequency ablation or surgical resection.
4. Patients who are unwilling to complete the study.
5. Patients with suspected unavailability throughout the study.
6. Arterio-portal shunts.
7. Vascular anatomy precluding correct catheter placement.
8. Presence of collateral vessels pathways potentially endangering normal territories during embolization.
9. Patients with non HCC malignancies (e.g. cancer colon metastasis).
10. Patients with extra-hepatic spread.

All included patients were subjected to,

1. Complete history taking.
2. Pre-procedural laboratory evaluation including: (LFTs, RFTs, CBC, INR, α-fetoprotein level, Viral markers).
3. Imaging including,

a- Pre-procedural triphasic computed tomography.
b- Angiogram (Before the procedure).
c- Procedure
Table 1: Patients’ Characteristics

| Item | Conventional TACE (n=24) | TACE | DEBs-TACE (n=16) | b P-value |
|------|--------------------------|------|------------------|-----------|
| A) General characters | | | | |
| 1-Age at TACE (years) (mean) | 64.2 ±3.1 | 65.1±3.0 | a 0.368 |
| 2-Sex (male/female) | 20/4 | 13/3 | 0.865 |
| 3-Smoking (Yes/no) | 12/12 | 9/7 | 0.69 |
| 4-Liver cirrhosis (Yes/no) | 22/2 | 14/2 | 0.66 |
| B) Child paugh stage | | | | |
| Child paugh A/B | 18/6 | 12/4 | 1.0 |
| C) Tumor characteristics | | | | |
| 1-Number of tumors (Unifo-cal/multifocal) | 5.5 ±2.5 (3-8) | 5.2 ±2.8 (2.4-8) | a 0.725 |
| 2-Largest tumor. (cm) (mean) | 2/22 | 1/15 | 0.806 |
| 3-Partial portal vein thrombosis (yes/no) | 13/11 | 8/8 | 0.79 |
| D) Causes of liver disease | | | | |
| 1-Hepatitis B | 3 | 2 | 1.0 |
| 2-Hepatitis C | 21 | 14 | |
| E) BCLC stage | | | | |
| -BCLC 0 | 1 | 0 | 0.58 |
| -BCLC A | 4 | 5 | |
| -BCLC B | 19 | 11 | |
| -BCLC C | 0 | 0 | |
| -BCLC D | 0 | 0 | |
| F) Performance status (ECOG) | | | | |
| -ECOG 0 | 15 | 10 | 0.53 |
| -ECOG 1 | 5 | 5 | |
| -ECOG 2 | 4 | 1 | |

a) Independent t-Test b Chi square test (X2)

Table 2: Tumor Response After 1 Month

| Variables | Conventional TACE (n=24) | TACE | DEBs-TACE (n=16) | P value |
|-----------|--------------------------|------|------------------|---------|
| Complete response (CR) | 6 (25%) | 4 (25%) | | |
| Partial response (PR) | 11 (45.8 %) | 8 (50 %) | 0.99 |
| Stable disease (SD) | 5 (20.8 %) | 3 (18.7%) | |
| Progressive disease (PD) | 2 (8.3 %) | 1 (6.2%) | |

Chi square test (X2)

*Conventional TACE: We used lipidol and adriamycin.
*DEB TACE: We used drug-eluting beads (Hepashere).
d-Angiogram (After the procedure)
e-Follow-up triphasic CT within 1 month.
4. Post-procedural laboratory evaluation including: LFTs and α-fetoprotein level.
5. Complications were recorded if present.

Approval was obtained from ethical Zagazig University Institutional Review Board (IRB).

Patients were divided into cTACE group and DEBS-TACE group according to the TACE regimen they received. Patients were diagnosed with HCC and they had a triphasic CT imaging within one month prior to their TACE procedure.

Patients were diagnosed with HCC either by the classic radiological features of a hepatic lesion with arterial phase enhancement, venous and delayed phases.
Table 3: Complications

| Items                        | Adverse event (yes/no) | C-TACE (n=24) | DEBs-TACE (n=16) | P-value |
|------------------------------|------------------------|---------------|------------------|---------|
| 1) Abdominal pain (yes/no)   | 18/6 (75 %)            | 6/10 (37.5 %) | 0.017*           |
| 2) Nausea and vomiting (yes/no) | 13/11 (54.17 %) | 3/13 (18.75 %) | 0.025*           |
| 3) Fever (yes/no)            | 8/16 (33.3 %)          | 3/13 (18.75 %) | 0.311            |
| 4) Fatigue (yes/no)          | 8/16 (33.3 %)          | 2/14 (12.5 %)  | 0.136            |
| 5) Bleeding/hematoma (yes/no)| 1/23 (4.17 %)          | 1/15 (6.25 %)  | 0.76             |
| 6) Ascites (yes/no)          | 2/22 (8.33 %)          | 1/15 (6.25 %)  | 0.806            |
| 7) Alopecia (yes/no)         | 8/16 (33.3 %)          | 1/15 (6.25 %)  | 0.044*           |

Chi square test (X2)

Follow up with triphasic CT imaging was obtained within 1 month after TACE. Tumor response rate after TACE was categorized according to the four categories of the mRECIST: complete response, partial response, stable disease or progressive disease. Complete response (CR) is defined as complete disappearance of tumor arterial enhancement. Partial response (PR) is defined as at least 30% reduction in the sum of the diameter of arterial enhancement in reference to baseline diameter. Progressive disease (PD) is defined as at least 20% increase in the sum of the longest diameter of the lesions in reference to baseline diameter. Stable disease (SD) is defined as a response that does not categorized as partial response or progressive disease categoryFigures 1 and 2. Complications were recorded if present.

Statistical analysis

1. Patient demographics, clinical history, laboratory data, and cross sectional imaging data were collected. Pre-TACE CT variables including number of lesions, size of tumors, and total axial diameter of the 3 largest tumors in the case of multifocal HCC were analyzed. Tumor response from post-TACE CT according to mRECIST criteria were recorded, Complications were recorded if present.The data were analyzed with proper statistical tests.

2. The collected data were coded, entered, presented, and analyzed by computer using a data base software program, Statistical Package for Social Science (SPSS) version 20.

3. Qualitative data were represented as frequencies and percents.

4. Chi square (X2) was used to detect relation between different qualitative variables.
**Figure 1: 61 y Old Patient with left lobe HCC**

(a) Left lobe shows faintly enhanced HCC

(b) HCC revealed washout in venous and delayed phases in triphasic CT study

(c) HCC revealed washout in venous and delayed phases in triphasic CT study

(d) Preoperative angiogram revealed classic anatomy: right hepatic artery, left hepatic artery and gastroduodenal artery

(e) Selective catheterization of left hepatic artery revealed pathological circulation of HCC and tumour blush

(f) Concentration of lipiodol and Adriamycin in HCC during injection

(g) Postoperative angiography revealed complete

(h) HCC is completely filled with lipiodol in arterial, venous
Figure 2: This patient was 66 years old came with large capsulated right lobe HCC and he received drug eluting beads
5. For quantitative variables mean and standard deviation were computed.
6. Independent t-test (t) was used for detection of difference between different quantitative variables.
7. The results were considered statistically significant and highly statistical significant when the significant probability (P value) was < 0.05*.

RESULTS AND DISCUSSION

Table 1 shows no significant difference between two groups regarding age or sex. The HCC were more common in old age males. HCC also were more common in cirrhotic liver. Smoking history was similar between both groups. Tumor characteristics were nearly similar between two groups, multifocal HCC were more common than unifocal HCC in both groups. Tumor size was ranging from 3 cm to 8 cm with mean diameter 5.5 cm in first group, and it was ranging from 2.4 cm to 8 cm with mean diameter 5.2 cm in second group, two cases with partial portal vein thrombosis (30%) were done by using conventional TACE, and one case with partial portal vein thrombosis (25%) was done by DEBs-TACE Figure 3. HCC occur on top viral infection to the liver, HBV and HCV, Cases with HCV were more common than cases with HBV in both groups. We carefully selected our patients as they were with BCLC 0, A, and B. In conventional TACE, one patient was with BCLC 0 (4.1%), 4 patients were with BCLC A (16.6%), and 19 patients were with BCLC B (79.1%). In drug eluting beads TACE, 5 patients were with BCLC A (31.25%), and 11 patients were with BCLC B (68.75%).

Table 2 We found that complete response was 6 cases (25%) in c TACE group, and 4 cases (25 %) in drug eluting bead TACE group, partial response was achieved in 11 cases (45.8%) in c TACE group, partial response was achieved in 8 cases (50 %) in DEBs-TACE group, Cases with stable disease were 5 cases (20.8%) in cTACE group, and it was 3 cases (18.7 %) in drug eluting bead TACE group, Progressive disease is noted in two cases (8.3%) in c TACE group, and one case (6.2%) in drug eluting TACE group. Objective response rate (ORR) was defined as percentage of patients who achieved complete response or partial response, for example ORR in follow up after 1 month, it was 70.8 % in c TACE group, and it was 75 % in drug eluting bead TACE.

There were no significant differences between two groups regarding tumor response after 1 month. Complications were as follow: 18 cases (75%) with abdominal pain in c TACE group, and 6 cases (37.5%) with abdominal pain in DEBs-TACE group, Nausea and vomiting were noted in 13 cases (54.17%) in c TACE group and in 3 cases (18.75%) in DEBs TACE group, Alopecia was noted in 8 cases (33.3 %) in c TACE group and in one case (6.25%) in DEBs TACE group. 8 cases (33.3%) with fever in c TACE group, and 3 cases (18.75%) with fever in DEBs-TACE group, 8 cases (33.3%) with fatigue in c TACE group, and 2 cases (12.5%) with fatigue in DEBs-TACE group, 2 cases (8.33%) with ascites in c TACE group, and 1 case (6.25%) with ascites in DEBs-TACE group.

From Table 3 Almost all complications were significantly lower in DEBs-TACE group than in c-TACE group especially with abdominal pain, nausea, vomiting and alopecia. The only complication which was higher in DEBs-TACE was hematoma (6.2 %), and it was (4.1 %) in c-TACE group.

The choice of TACE regimen and the value of using the more expensive drug eluting beads is still debated, and is often based on the doctor’s bias or his experience, despite the proposed benefits of DEBs, there is limited and conflicting data on the efficacy of DEBs-TACE compared to conventional TACE. We performed this prospective comparative study between conventional TACE and DEBs-TACE in order to overcome bias towards using one of the two regimens, our data revealed no significant difference between the two groups regarding tumour response, but there is less complications rate in DEBs-TACE group.

In our clinical study, there was no significant difference between two groups regarding patients characteristics, no significant difference in age, sex, smoking history or liver cirrhosis between two groups. Both groups were nearly have same percentage of patients in child paugh stage A and child paugh stage B, no significant difference was found regarding number of tumours, largest tumour size and bilobar versus unilobar tumours. HCC occur on top viral infection to the liver, HBV and HCV, Cases with HCV were more common than cases with HBV in...
both groups. We carefully selected our patients, they were with BCLC 0, A, and B, we excluded BCLC C & D to minimize occurrence of complications as possible as we can.

There were no significant differences between two groups regarding tumor response after 1 month. Li et al. did a comparative study which revealed no difference of complete response was found between DEB-TACE group (14.3%) and cTACE group (5.1%)(P=0.167), however, the objective response rate (ORR) was increased in DEB-TACE group (73.8%) than that incTACE group (41%)(P=0.003) (Li et al., 2019).

We found that our results were partially agree with that study regarding no difference in complete response in between two groups, however objective response rate in our study was also of no significant difference in contrary to their study, this difference may be due to their sample size which was (81) HCC patients, (42) with DEB-TACE, (39) with cTACE, this number was double our sample size, it can reveal small differences in ORR in between groups. FerrerPuchol et al (2011), did a similar comparative study and found no difference in complete response in between two groups of patients. Malensteina et al (2011), did a similar comparative study and found no difference in complete response in between two groups of patients, and he also did his study on small sample size, (14) patients did cTACE and (16) patients did DEB-TACE.

Despite theoretical advantages of DEB-TACE, it is still controversial in clinical practice as to whether DEB-TACE is superior to cTACE in regard to overall survival and treatment response, recently reported meta-analysis showed that the two modalities represent comparable results, suggesting an absence of difference in tumor response between DEB-TACE and cTACE (Song and Kim, 2017).

Complications rate was less in DEBs TACE group, this was justified by its mechanism of action leading to slow rhythmic release of chemotherapy, leading to lower plasma concentration level and less complications, significant difference was noted with abdominal pain, vomiting and alopecia. The only complication which was higher in DEBs-TACE was hematoma (6.2 %), and it was (4.1 %) in c-TACE group, this was due to small size of the sample as both results were due to involvement of one patient, and the justification was that occurrence of hematoma was depending on coagulable status of patient not depending on systemic concentration of chemotherapy.

There was a clinical trial done in Italy comparing between two procedures, it concluded that DEB-TACE and the cTACE are equally effective and safe, with the only advantage of DEB-TACE being less postprocedural abdominal pain (Golferi et al., 2014).

Varela et al., (Varela et al., 2007) firstly reported that systemic concentrations of doxorubicin were significantly lower in patients treated with DEB-TACE than patients treated with cTACE. This result was verified by Poon et al., (Poon et al., 2007) who performed DEB-TACE with possibly the highest dose of doxorubicin (150 mg). Both studies showed that none of treated patients exhibited doxorubicin-related systemic toxicity (alopecia, bone marrow suppression, or dyspnea) (Varela et al., 2007; Poon et al., 2007). The DEB-TACE group showed a significant decrease in chemotherapeutic agent-related systemic and liver toxicity compared to the cTACE group (Song and Kim, 2017).

In comparison with cTACE, DEB-TACE facilitates higher concentrations of drugs within the target tumor and lower systemic concentrations. Despite the theoretical advantages of DEB-TACE, it is still controversial in several clinical studies as to whether DEB-TACE is superior to cTACE in terms of efficacy. However, it seems that DEBTACE shows at least similar clinical outcomes and less adverse events than c TACE (Song and Kim, 2017). Strength in our study that it is real life comparative prospective clinical trial, it enables evaluation of the two methods in clinical practice with Egyptian patients.

There were still several limitations to this study as,

1. This was a single center experience.
2. The sample size in our study was relatively small which might reduce statistical power.
3. The follow up time was rather short to observe survival profit of patients, which should be prolonged in the future studies.
4. Lack of randomization, which may lead to some selection bias.

CONCLUSIONS

Trans-arterial chemoembolization is considered the standard management for intermediate-stage HCC. Moreover, it is recognized as the most common bridging therapy offered to patients on a waiting list for liver transplantation. Variations in TACE protocols are vast. A wide range of chemotherapeutic mixtures have been reported in the literature like bland embolization, chemoembolization and
chemoperfusion. Initially, transarterial therapy for HCC was performed using bland embolization. Conventional TACE has been used for years with the gold standard mixture composed of Lipiodol mixed with chemotherapeutic agents, most commonly Doxorubicin. Recently, Drug eluting beads are appearing as new drug. Drug eluting beads have been introduced and marketed as a better chemotherapeutic carrier and embolic agent. The mechanism of DEBS action is achieved through prolongation of the contact time between chemotherapeutic agents and tumor cells with sustained slower release of chemotherapeutic agents, which leads to lower peak plasma concentrations/systemic toxicity and theoretically greater tumor toxicity. Despite these proposed benefits of DEBS, there is limited and conflicting data on the efficacy of DEBS-TACE compared to cTACE. The current study represents comparative clinical trial between two groups of patients, 1st group represents conventional TACE, we used (lipidol as embolizing agent mixed with Doxorubicin), 2nd group represents DEBs-TACE, we used drug eluting beads. Statistical analysis of our results showed no significant difference between two groups regarding tumour response, however there was significant reduction in complications in DEBs-TACE group compared to c TACE group. Using drug eluting beads can minimize complications rate, however its cost is still limiting factor as many patients can not afford it, we recommend using DEBS-TACE in large capsulated lesions, as this can result in better tumour response. Further multi-center randomized controlled clinical trials with larger sample size are recommended to address the tumour response, complications rate, liver status and changes in α-fetoprotein level to overcome current study limitations.

ACKNOWLEDGEMENT

I would like to thank professor Dr. Mohamed I. Teama, Professor of Radiodiagnosis, Zagazig University, for his help and great support in the completion of this work.

Conflict of Interest

The author declared that there is no conflict of interest.

Funding Support

None.

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