Comparison of Outcomes with Triple-Regimen versus Double-Regimen Transarterial Chemoembolization

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Abstract

We sought to evaluate differences in outcomes between double versus triple transarterial chemoembolization (TACE). TACEs over a 1-year period were retrospectively reviewed and divided into two groups: double and triple. Imaging response and complications were made on a per-procedure basis. Student's *t*-test was used to calculate differences in continuous variables, and chi-square test was used to calculate differences in categorical values.Overall tumor response was similar between the two groups, and there were no significant differences in complications between groups. Outcomes are similar between double and triple conventional TACE, suggesting that adding a third drug may only contribute to cost.

Keywords
- TACE
- chemoembolization
- regimen
- dual therapy
- triple therapy

Transarterial chemoembolization (TACE) is an accepted form of liver-directed therapy and is established in liver cancer treatment guidelines such as the Barcelona Clinic Liver Cancer (BCLC).[1] Such guidelines are predominantly based on two landmark clinical trials that established TACE as beneficial treatment for hepatocellular carcinoma (HCC) over best supportive care.[2,3]

Since being established as effective therapy, the specific chemotherapeutic agents for transarterial delivery have varied and were generally extrapolated from systemic chemotherapy regimens. The landmark trials of Llovet et al and Lo et al establishing TACE within liver cancer treatment paradigms each used a single-agent chemotherapeutic regimen, which was different between studies—cisplatin in one[3] and doxorubicin in the other.[2] Several retrospective studies have reviewed outcomes comparing the use of different chemotherapy agents and embolic materials for TACE with reports yielding inconsistent conclusions between studies.[4–7] Within the United States, "conventional" TACE (cTACE) is widely considered to be an emulsion consisting of doxorubicin, mitomycin, and cisplatin mixed with lipiodol.

The availability of cisplatin powder became critically short and was unavailable at our institution around March 2011 (internal email communication). Cisplatin powder returned to inventory at our institution in 2019 (internal email communication). During this period of cisplatin unavailability, many operators transitioned to using simply doxorubicin and mitomycin as the cTACE regimen. When cisplatin returned to the commercial market, the decision to use double or triple agent cTACE was based on contraindications to administering cisplatin such as renal impairment or otherwise mainly left to the discretion of the performing physician. Given the current healthcare environment, avoiding additional cost, such as by adding a third drug to a treatment regimen, is an important factor to consider.

The purpose of this study was to evaluate outcomes for double- versus triple-regimen TACE. Specifically, we sought

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to evaluate imaging response and early adverse events relative to each regimen.

Materials and Methods

Study Design and Participants

A retrospective review of all chemoembolization procedure codes recorded at a single institution between July 1, 2019, and June 30, 2020, was performed. IRB approval was obtained with waiver of informed consent.

A total of 110 procedures in 82 patients were reviewed. TACE performed as part of planned combination therapy with percutaneous ablation and/or radioembolization and those performed as repeat locoregional therapy to the same tumor or artery were excluded from analysis. This yielded a final study cohort of 58 chemoembolization procedures performed in 50 patients for analysis on a per-procedure basis. The study cohort was divided into "double-" and "triple-"regimen TACE groups. The double group consisted of patients who underwent TACE with a chemotherapy emulsion of doxorubicin 50 mg and mitomycin 10 mg with lipiodol. In the triple group, patients underwent TACE with a mixture of doxorubicin 50 mg, mitomycin 10 mg, and cisplatin 100 mg combined with lipiodol. Emulsions were mixed as "water in oil." Use and type of additional bland embolics (polyvinyl alcohol or tris-acryl gelatin particles) were at the discretion of the performing physician. Drug-eluting bed TACE procedures were not included in this cohort.

The electronic medical record (EMR; Epic, Madison, WI) was reviewed for clinical details in all cases. Pre-, intra-, and postprocedural imaging were reviewed via PACS (McKesson, Alpharetta, GA).

Clinical Outcomes and Laboratory Parameters

The EMR was reviewed for demographic data, including age, gender, diagnosis, indication for treatment, Model for End-Stage Liver Disease score and Child–Pugh score at the time of procedure, and history of transjugular intrahepatic portosystemic shunt. Additionally, postprocedural complications and laboratory parameters obtained at 1-month postprocedure follow-up were reviewed. Documented complications were reviewed and recorded.

Imaging Outcomes

Posttreatment imaging (targeted at 1 month postprocedure and subsequently every 3 months) was reviewed for tumor response and evidence of portal vein, hepatic vein, arterial thrombosis, hepatic infarct, biloma formation, or other indications of biliary injuries at all available follow-up time points until the time of data censure. Data were censored at the time of study data collection or on the date of repeat treatment or response failure, whichever came first. Censure at repeat treatment or response failure allowed for analysis of tumor response on a per-tumor and per-treatment basis. Treatment response of the targeted lesion was categorized according to mRECIST and performed on a per-procedure basis.

Statistical Analysis

Student's *t*-test was used to analyze differences in continuous values between groups. Chi-square test was performed to calculate differences in categorical values between the groups. $p < 0.05$ was considered statistically significant.

Results

Demographics

There were no significant differences between study group populations. Specifically, there were no differences in average age or degree of liver dysfunction. The majority of patients were Childs–Pugh A. Only two patients were Childs–Pugh C and both were in the triple group. The tumor type in the majority of cases in both cohorts was HCC (►**Table 1**). Other tumor types were cholangiocarcinoma ($n = 1$ in the double group) and metastatic neuroendocrine ($n = 3$ in the double group, and $n = 6$ in the triple group).

Procedural Details

Of 58 total procedures, there were an approximately equal number of cases in each study group. Specifically, 30 of 58 (51.7%) procedures were in the double group and 28 of 58 (48.3%) were in the triple group. Multifocal tumor was treated in 13 of 30 cases in the double group and 18 of 28 cases in the triple group. Six of 30 cases in the double group and 2 of 28 cases in the triple group had portal vein occlusion or invasion. The majority of procedures were performed selectively in a segmental fashion. Segmental TACE was performed in 23 of 30 procedures in the double group and 17 of 28 in the triple group.

Table 1 Study cohort demographics

	Double	Triple	*p*
Study group (*n*)	30	28	
Males (*n*)	19	20	0.158
Age (mean)	63 (±10.5)	63 (±9.1)	1
MELD (mean)	11.1 (±4.6)	11.3 (±5)	0.87
Child–Pugh A (*n*)	19	11	0.364
Prior TIPS (*n*)	3	3	0.929
HCC (*n*)	26	22	0.415

Abbreviations: HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

Table 2 Treatment response related to TACE regimen

Treatment response	Double ($n = 30$)	Triple ($n = 28$)
Complete response	8 (26.7%)	13 (46.4%)
Partial response	13 (43.3%)	7 (25%)
Stable disease	8 (26.7%)	7 (25%)
Progressive disease	1 (3.3%)	1 (3.6%)

Abbreviation: TACE, transarterial chemoembolization. Note: p = 0.393.

Table 3 Complications by type related to TACE regimen

Complication	Double ($n = 30$)	Triple ($n = 28$)
PES	7 (23.3%)	10 (35.7%)
AKI	3 (10%)	2 (7.1%)
Biliary	2 (6.7%)	1 (3.6%)
PVT	5 (16.7%)	3 (10.7%)

Abbreviations: AKI, acute kidney injury; PES, postembolization syndrome; PVT, portal vein thrombosis; TACE, transarterial chemoembolization.
Note: $p = 0.674$.

Superselective TACE was performed in 7 of 30 procedures in the double group and 2 of 28 in the triple group. Lobar TACE was performed in 9 of 28 in the triple group.

Tumor Response

Tumor response was not significantly different between groups ($p = 0.393$; ►**Table 2**). Specifically, overall response rate (complete response [CR] and partial response [PR]) was greater than nonresponse (stable disease and progressive disease [PD]) in both the triple and double groups. The overall response rate (CR and PR) was also similar between both study groups (21/30 or 70% in the double group and 20/28 or 71.4% in the triple group). PD was very low with only one case in each group. Median follow-up time was 4 months (range: 1–16 months) in the double group and 2 months (range: 1–13 months) in the triple group (not statistically significant).

TACE-Related Complications

Overall, there were no differences in complications between groups. Specifically, there were no significant differences between groups in types of complications ($p = 0.674$; ►**Table 3**). In both groups, the most common complications were postembolization syndrome. Biliary complications were very low with only one case of biloma in each group and only one biliary stricture noted only in the double group. There was no difference in the occurrence of bland portal vein thrombosis between treatment groups.

Discussion

TACE is an established treatment for liver tumors, particularly intermediate-stage HCC. We sought to evaluate differences in outcomes of cTACE when using a triple drug regimen (doxorubicin, mitomycin, and cisplatin) versus a double drug regimen (doxorubicin and mitomycin). The present study demonstrates no difference in the incidence of adverse events or in tumor response with the use of either double- or triple-regimen TACE.

Despite general consensus that the definition of cTACE is a particular triple drug regimen, there is little scientific evidence to establish a specific combination of drugs for delivery in chemoembolization. In fact, the landmark studies establishing TACE as accepted therapy for HCC used different single-agent regimens.[2,3] There have been several studies evaluating different regimens with mixed results. A retrospective single-center study demonstrated superior efficacy, specifically in terms of imaging response, of triple-regimen TACE compared with single-agent TACE without differences in complications between groups, although toxicities were not tracked and reported.[5] A prospective study evaluating triple therapy TACE with or without embolization and single-agent TACE suggested a survival benefit with triple therapy regardless of embolic delivery.[6] Neither study addressed the intermediary double-agent TACE nor evaluated differences in complications between treatments. Another prospective study evaluating single-, double-, and triple-agent TACE concluded that multidrug regimen may improve tumor response and survival.[8]

Yet, other studies report no benefit of chemoembolization using more than a single agent. A single-center study evaluating the addition of gemcitabine to mitomycin did not demonstrate a difference in survival or imaging response.[4] However, another retrospective study of single-agent versus triple-agent TACE did not demonstrate a difference between regimens in imaging treatment response but did suggest a survival advantage in the single-agent group, even when stratified by liver dysfunction.[9] This study also evaluated toxicities and noted alterations in only liver chemistries to be greater in the triple-regimen group.

With the return of cisplatin to our institution's inventory, performing triple-regimen TACE with cisplatin, mitomycin, and doxorubicin again became possible. Generally, cisplatin is avoided in patients with prior adverse reactions to platinum-based agents and in patients with renal dysfunction as it is renally excreted.[10] Aside from these contraindications, operators may choose not to add it to the chemotherapy mixture for TACE due to preference. On the other hand, adding a third drug to the treatment regimen could add unnecessary cost to the treatment and procedure. We sought to evaluate whether outcomes varied between the different regimens. In this limited review, there were an approximately equal number of double- and triple-regimen TACE procedures performed, and we found that there were no differences in terms of overall tumor response or complications following either regimen. This suggests that when cisplatin cannot be added due to patient contraindications, such as renal impairment, there is no detriment to treatment efficacy. Likewise, the addition of a third cytotoxic chemotherapeutic does not appear to increase the incidence of adverse events following TACE.

Our results differ from the study by Mouli et al which reported improved survival associated with single-drug

TACE and increased complications with triple-drug TACE.[9] However, their study was conducted over a lengthy period of time (14 years) during which indications and techniques for transarterial therapy evolved, which complicates interpretation of their results. In fact, their reported results could merely be due to better patient selection and improved technical factors such as selectivity of treatment delivery over time as they also report that the majority of procedures performed in the later part of the study period were with the single drug regimen as a result of the cisplatin shortage. In contrast, our study analyzed data over a short and recent time period during cisplatin availability where overall factors should be similar between groups except for whether double drug or triple drug emulsion was delivered. We could not evaluate a survival effect in this study due to the short time frame of study precluding long-term follow-up.

Overall, our experience is on par with prior reported meta-analyses demonstrating efficacy and safety of TACE. Specifically, we reported postembolization syndrome as the most common complication of TACE regardless of regimen which was also seen on meta-analysis studies.[11] Our response rate compares favorably with or better than other reports at approximately 70% for both study groups.[4–6,9]

Limitations of this study include its retrospective nature with potential for operator bias toward a particular treatment strategy, including patient selection for TACE and chemotherapeutic regimen. This study was not controlled for tumor burden or disease severity, and analyses were performed on a per-procedure basis. Due to this and the short follow-up for this selected cohort, survival analysis was not performed. Lastly, operator differences in emulsion ratios and use of embolics during TACE could have confounded outcomes.

Conclusion

Our data indicate no difference between double- and triple-regimen TACE in outcomes, both in terms of tumor response and adverse events. This suggests that the decision to deliver TACE with or without cisplatin, whether due to contraindications or operator preference, may not influence treatment efficacy or incidence of complications but could impact cost of treatment depending on the number of drugs used.

Note

This work was presented at the Society of Interventional Oncology Annual Meeting 2021.

Conflicts of Interest

A.R.S. reports grants from RSNA R&E Research Foundation and NeuWave Medical, honoraria from NeuWave Medical, stock/stock options from HistoSonics Inc, and advisor agreement with HistoSonics Inc.

O.D. declares no conflict of interest.

W.S.R. reports consulting fees from Sirtex, Boston Scientific, BD/Bard, Terumo, and Varian and board membership with the Society of Interventional Oncology.

P.J.P. reports consulting fees from Boston Scientific, Medtronic, Penumbra, and Cordis and leadership role with the Society of Interventional Radiology.

E.J.H. declares no conflict of interest.

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M.J.S. declares no conflict of interest.

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