Role of Trans-Arterial Chemoembolization (TACE) in patients with hepatocellular carcinoma

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Abstract. – OBJECTIVE: One of the most frequent types of primary liver cancer is hepatocellular carcinoma (HCC). Due to the high incidence of hepatitis B infection, HCC accounts for about 5% of all cancers. HCC is indeed one of the largest leading causes of cancer deaths in the world and the third biggest cause of cancer-related death. The purpose of our research was to see how effective TACE (Trans-Arterial Chemoembolization) therapy was in those who had hepatocellular cancer.

MATERIALS AND METHODS: The Preferred Reporting Items for Systematic Reviews (PRISMA) statement was used to conduct the systematic review. From their inception through the first week of January 2022, the following electronic databases were thoroughly searched: PubMed, Embase, PsycINFO, and the Cochrane Library, with no language constraints. The search terms were “transarterial chemoembolization” or “chemoembolization” or “TACE” AND “hepatocellular carcinoma” or “hematoma” or “HCC” or “liver cancer” or “liver tumor” AND “sorafenib”. The references of the discovered articles were also examined. The search included English papers with adult patients only.

RESULTS: A total of 1,234 studies were found for screening after searching the literature in multiple databases. 767 papers were removed based on titles and abstracts, but the complete text of the remaining 129 publications was full text and eligible. In total, 13 studies were included in this research. The study’s screening flowchart was depicted using the PRISMA technique. The majority of the findings was of a small magnitude. Even with chronic liver disease and huge tumor groupings, they agreed on the safety and efficacy of such multiple closures prior to plan resection (50 mm). Even after curative resection, the prognosis for these patients remains poor because of portal vein thrombosis, high frequency of liver failure, and microscopic tumor thrombosis.

CONCLUSIONS: TACE is a low-cost palliative treatment for HCC. The initial tumor size is an independent predictor of survival.

Key Words: Hepatocellular carcinoma, TACE, Transarterial chemoembolization, Hepatitis, Carcinoma.

Introduction

Hepatocellular carcinoma is a common primary liver malignancy (HCC). It is linked to cirrhosis, which is caused by alcohol and viruses. Due to the high frequency of hepatitis B, HCC accounts for 5% of all malignancies. Cancer-related mortality is the third main cause of death from HCC (after stomach and lung cancer). Hepatitis C infection is rising, and so is HCC. Chronic hepatitis B infection, which accounts for over 80% of cases globally, significantly influences demography. Asia has the greatest incidence. In Western nations, the rate is lower, and alcohol is more prevalent1-4. The 5-year cumulative risk of hepatitis B (HBV) infection is 10%, Hepatitis C (HCV) infection is 30%, alcoholism is 8%, and biliary cirrhosis is 5%. Other risk factors: food toxins, e.g., aflatoxins, Congenital biliary atresia, Metabolism inborn error, Diabetes mellitus, obesity, and Cholestatic syndrome4.

Hepatocellular carcinoma is more frequent in men and is detected in late middle age or elderly people with an average age of 65 (75% cases). The tumor may also afflict children; in fact, behind hepatoblastomas, it is the second most frequent primary liver cancer in children. Hepatocellular carcinoma (HCC) is typically detected late in the course of the illness when symptoms and liver damage have already occurred. Virtually, no viable medication would increase survival at this late stage5,6. Furthermore, the treatment-related morbidity is too high. TACE is one of the most common first treatments for loco-regional HCC and tumors that do not meet the criteria. TACE was chosen because of HCC’s neoangiogenic capabilities and mode of action on the tumor’s hepatic arterial supplies. Throughout the tumor’s early phases of development, the portal system supplies blood flow. Even the best HCC relies on hepatic artery supply.
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since the tumor grows in size. This tumor feature represents the pathologic foundation for the radiologic HCC criteria. The hepatic artery branch is severed, causing hypoxia and necrosis. This is performed by using an image-guided catheter-based particle infusion to reduce arterial blood flow dramatically. A chemotherapeutic drug is injected before vascular embolization. Doxorubicin, cisplatin, mitomycin, and epirubicin have all been utilized in the past as chemotherapy drugs. Additionally, doxorubicin-eluding beads have recently emerged as a promising TACE substitute. Drug-eluding beads are expected to enhance both treatment response rates and tumor necrosis as compared to conventional TACE. TACE had an 82% 1-year survival rate and a 63% 2-year survival rate for unresectable HCC, according to Lau et al. TACE response is an independent predictor of survival. After two years, TACE-treated patients exhibited a 20-60% increase in survival. Post-embolization syndrome symptoms include stomach discomfort, nausea, ileus, and fever. TACE treatment has previously been deemed contraindicated in portal vein tumor thrombosis. Combined with a tumor thrombus-induced portal vein blockage, this hepatic arterial blood flow disruption may produce severe hepatic necrosis. Several prospective and retrospective studies have indicated that TACE improves overall survival in cirrhotic HCC patients with portal vein tumor thrombosis. TACE and Sorafenib may also work synergistically.

Materials and Methods

The systematic review was carried out using the Preferred Reporting Items for Systematic Reviews (PRISMA) statement. In addition, a thorough search of the different electronic databases was done from their establishment through the first week of January 2022: PubMed, Embase, PsycINFO, and the Cochrane Library, without language restrictions. The search terms were “transarterial chemoembolization” or “chemoembolization” or “TACE” AND “hepatocellular carcinoma” or “hematoma” or “HCC” or “liver cancer” or “liver tumor” AND “sorafenib”. The references of the articles that were found were also checked. Only English papers with adult patients were included in the search.

Inclusion and Exclusion Criteria

Sorafenib plus TACE-focused studies as a combination therapy in unresectable HCC were considered. Adult patients and English publications were the only subjects of the studies. All of the following variables were required: overall survival (OS), adverse events (AEs), time to progression (TTP), disease control rate (DCR), and tumor response.

Studies that looked at the effectiveness of Sorafenib alone as a combo treatment were excluded. Editorials, letters, case reports, meta-analyses, and reviews in languages other than English were not examined. Studies that were irrelevant to our issue or did not provide useful information were omitted.

Following the initial discovery of papers from databases, two researchers examined abstracts and titles to screen studies for the above-mentioned criteria. The number of studies and the grounds for exclusion were documented at each screening step. Following that, an independent reviewer read the whole text of the work to be published and gathered pertinent information, such as treatment methods, baseline characteristics, TTP, OS, AEs, DCR, tumor responses, and HR. Finally, all data were gathered and analyzed. The two researchers’ disagreements were discussed until a solution was found.

TTP was referred to as the period between the commencement of therapy and the final follow-up. The OS was computed from the first TACE through the date of death or the last follow-up. By integrating the partial response rate, stable sickness rate, and complete response rate, the DCR was created. Our meta-analysis focused on two forms of TACE: drug-eluting beads TACE (DEB-TACE) and traditional TACE (c-TACE). Combination therapy was classified as a treatment that included TACE before or after Sorafenib. During their treatment, patients should have at least one TACE session. Data was collected and evaluated separately using predesigned data extraction forms. The information was entered into the Cochrane review manager program.

Results

A total of 1,234 research articles were found for screening after searching the literature in different electronic databases. 767 papers were removed based on titles and abstracts, but the complete texts of the remaining 129 publications were full text and eligible. In total, 13 articles were considered in this research. The study’s screening flowchart is depicted using the PRISMA technique (Figure 1).
All patients were assigned to one of two Child-Pugh (CP) classes: A or B, with CP A being the most common (65-94%). BCLC B stage patients were recorded at about 20-100%, and the percentage of patients with BCLC C stage was between 1.9-80%. The performance level of the ECOG was reported to be 0 or 1 (94-100%). Hepatitis virus infection rates ranged between 24 and 100% in total. Table I lists all patients’ baseline data, as well as the length of sorafenib treatment and the number of TACE sessions.

Prior to commencing Sorafenib, the patients were TACE-responsive. Some people in Ohki et al. study did not respond to TACE. Each trial’s treatment techniques are also outlined in Table I. Table II displays the HR for TTP from nine studies. The overall HR for TTP was 0.66 (95% confidence interval (CI) 0.50-0.81, \( p \)-value = 0.002), showing that combination treatment substantially lengthened TTP, according to the forest plot. These findings could indicate that Asian countries have a significant positive TTP outcome. Disparities in survival outcomes between locations may be due to a variety of causes.

The most important conclusions of the research were of minimal importance. They concurred on the effectiveness and safety of such double occlusion prior to plan resection, even in the chronic liver disease and big tumor (50 mm) groups. The prognosis for these patients remains poor even after curative resection owing to the frequent occurrence of portal vein thrombosis, liver failure, or microscopic tumor thrombosis. We conclude that a lack of response after two consecutive TACE operations led to a poor OR, regardless of whether or not the TACE treatment was repeated.

Figure 1. The PRISMA technique was used to create a schedule of records pertinent to the current study.
**Table I. Baseline characteristics of study and patients.**

<table>
<thead>
<tr>
<th>SN.</th>
<th>Author references</th>
<th>No. of Participants</th>
<th>Study Design</th>
<th>Region</th>
<th>Etiology</th>
<th>No. of TACE</th>
<th>Treatment</th>
<th>Duration Time of orafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Erhardt et al11</td>
<td>38</td>
<td>Phase II</td>
<td>Germany</td>
<td>NA</td>
<td>2.0 (mean)</td>
<td>TACE is the only time when continuous Sorafenib is discontinued.</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Pan et al12</td>
<td>41</td>
<td>Retrospective</td>
<td>China</td>
<td>HBV 97.6%, HCV 2.4%</td>
<td>2.0 (median)</td>
<td>Sorafenib was administered three days following the initial TACE operation.</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Cosgrove et al13</td>
<td>50</td>
<td>Phase II</td>
<td>USA</td>
<td>HBV 8%, HCV 44%</td>
<td>2.0 (median)</td>
<td>Sorafenib was begun one week prior to the first cycle of DEB-TACE.</td>
<td>1.5 Month</td>
</tr>
<tr>
<td>4</td>
<td>Ohki et al14</td>
<td>95</td>
<td>Retrospective</td>
<td>Japan</td>
<td>ST: HCV 75.0%, T:HCV 67.6%</td>
<td>2.0 (median)</td>
<td>Sorafenib was initiated two weeks after TACE.</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Yao et al15</td>
<td>150</td>
<td>Prospective</td>
<td>China</td>
<td>ST:HBV 84%, T:HBV 83%</td>
<td>2.0 (median)</td>
<td>Sorafenib therapy was started one week before or after the first TACE treatment.</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>Zhang et al (2016)16</td>
<td>20</td>
<td>Retrospective</td>
<td>China</td>
<td>HBV 80%</td>
<td>2.0 (median)</td>
<td>Sorafenib was administered 4-7 days before or after the TACE session.</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>Varghese et al17</td>
<td>124</td>
<td>Retrospective</td>
<td>India</td>
<td>B:HBV 37.3%, HCV 18.7% C:HBV 26.2%, HCV 23%</td>
<td>2.0 (median)</td>
<td>Sorafenib was started 5 days after TACE.</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>Wan et al18</td>
<td>450</td>
<td>Retrospective</td>
<td>China</td>
<td>NA</td>
<td></td>
<td>Oral Sorafenib was given either before or after TACE.</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>Sieghart et al19</td>
<td>15</td>
<td>Phase I</td>
<td>Austria</td>
<td>HBV 4%, HCV 20%</td>
<td>3.0 (median)</td>
<td>Sorafenib began two weeks before the first TACE</td>
<td>5.2 months</td>
</tr>
<tr>
<td>10</td>
<td>Chung et al20</td>
<td>151</td>
<td>Phase II</td>
<td>China and South Korea</td>
<td>NA</td>
<td>2.1 (mean)</td>
<td>Sorafenib Begun 4-7 days after TACE</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>Pawlik et al21</td>
<td>35</td>
<td>Phase II</td>
<td>USA</td>
<td>HCV 37%</td>
<td>2.0 (median)</td>
<td>One week before DEB-TACE, a week of continuous Sorafenib was started.</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>Dai et al22</td>
<td>119</td>
<td>Retrospective</td>
<td>China</td>
<td>PVTT with HCC</td>
<td></td>
<td>Postoperative treatment</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>Terasawa et al23</td>
<td>55</td>
<td>Prospective</td>
<td>France</td>
<td>Large HCC simultaneous</td>
<td></td>
<td>Preoperative treatment</td>
<td>NA</td>
</tr>
</tbody>
</table>
refractoriness, as defined by treatment criteria, seems to be supported by these data.

Considering that there was no substantial difference in survival between the initial CR group and the delayed CR group, we believe that repeated TACE is necessary to achieve CR, resulting in a survival advantage even in later TACE sessions. Individuals who initially exhibited an OR had a substantially greater survival rate than others who did not display an OR after repeated TACE, trailed by patients who demonstrated an OR in consecutive TACE sessions. This indicates that if an OR to TACE occurs, it is suggested to repeat TACE for survival purposes; however, if an OR does not exist twice in a row, additional TACEs may be superfluous.

Discussion

TACE is the most often utilized therapeutic option in those who have hepatocellular carcinoma (HCC) and are not candidates for therapeutic options. The rest of the world has a unique epidemiological heterogeneity when it comes to the etiology and stage of HCC at diagnosis; Asia and Africa contribute to over 80% of HCC cases.

Despite the fact that cirrhosis is the most prevalent cause of HCC, the etiology of cirrhosis has been found to affect HCC patients’ prognosis. This was not taken into account in every suggestion or prognostic assessment. HBV is to blame for 54.4% of all HCC cases found globally, while HCV is to blame for 31.1%. A small percentage of HCV-infected patients, however, are drinkers. Zhou et al. reported on the impact of viral hepatitis on survival in a meta-analysis of 4,744 patients, 2,008 of whom were HBV positive and 2,222 of whom were HCV positive, whereas 514 were HBV and HCV negative. When compared to patients with negative serology, those with viral hepatitis had a dismal prognosis. They also advocated for the use of adjuvant antiviral therapy after HCC treatment to prevent tumor recurrence.

HCV-related HCC, on the other hand, is more common in countries such as Japan, Spain, and others. Most of our patients (66/73; 90.41%) were symptomatic at presentation and had a somewhat large tumor size at the outset, indicating advanced illness. The treatment of these folks was incredibly tough. People with smaller tumors were included in Japan’s largest documented TACE experience, with a research sample of 8510 patients (24% with 2 cm and 75% with 5 cm). TACE’s utility in treating bigger liver tumors has received little attention (mean diameter approximately 7 cm).

SPACE was the first large-scale multinational randomized controlled study of Sorafenib or placebo in conjunction with TACE for intermediate-stage HCC. It revealed no significant difference in TTP between the combination treatment and TACE alone groups. Following that, a flood of clinical trials conducted around the world assessed the efficacy of combination medicine, with the vast majority concluding that it was more effective in terms of TTP than monotherapy. The majority of the comparative studies we reviewed discovered that, as compared to TACE alone, combining TIPS with Sorafenib increased TTP in patients who were not responding to TACE.

<table>
<thead>
<tr>
<th>SN.</th>
<th>Authors years</th>
<th>Combination group (95% CI)/months</th>
<th>HR (95% CI)</th>
<th>TACE alone group (95% CI)/months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sansonno et al</td>
<td>9.2</td>
<td>2.5 (1.66-7.56)</td>
<td>4.9</td>
</tr>
<tr>
<td>2</td>
<td>Zhang et al</td>
<td>4.9 (3.7-6.0)</td>
<td>NA</td>
<td>2.4 (1.3-3.4)</td>
</tr>
<tr>
<td>3</td>
<td>Bai et al</td>
<td>6.3</td>
<td>0.6 (0.422-0.853)</td>
<td>4.3</td>
</tr>
<tr>
<td>4</td>
<td>Hu et al</td>
<td>2.6</td>
<td>0.62 (0.47-0.82)</td>
<td>1.9</td>
</tr>
<tr>
<td>5</td>
<td>Huang et al</td>
<td>5.4</td>
<td>0.99 (0.67-1.47)</td>
<td>3.7</td>
</tr>
<tr>
<td>6</td>
<td>Lencioni et al</td>
<td>5.6</td>
<td>0.797 (0.588-1.08)</td>
<td>5.5</td>
</tr>
<tr>
<td>7</td>
<td>Muhammad et al</td>
<td>NA</td>
<td>0.93 (0.45-1.89)</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>Ohki et al</td>
<td>6.3</td>
<td>0.38 (0.22-0.63)</td>
<td>3.5</td>
</tr>
<tr>
<td>9</td>
<td>Yao et al</td>
<td>10.2</td>
<td>0.403 (0.251-0.646)</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Table II. Median Time to progression, the hazard ratio and 95% confidence intervals for the combined therapy group against the TACE alone group.
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In a small prospective case-control study, Zhao et al. treated 48 patients with inoperable HCC using PVTT. TACE was used in combination with PVCE in 23 of them, while TACE was used alone in the remaining patients. The TACE+PVCE group had a significantly greater rate of PVTT decrease, and the combination treatment also alleviated gastrointestinal symptoms more effectively ($p$-value = 0.05). During the 1-year follow-up, the survival rate also improved (48% vs. 25%, $p$-value = 0.05). Further research comprised 116 PVTT HCC patients who were administered with TACE alone (64 patients) or TACE with PVE (52 patients) and monitored for a longer period of time. The combination therapy group had a significant prognostic benefit, according to the findings. The advantages were underlined even more in patients with Type-I PVTT, where tumor thrombi were restricted to partial branches of the portal vein or above it, according to the subgroup analysis.

In clinical trials involving HCC patients with portal venous invasion, combination treatment was shown to be more effective than TACE alone in terms of TTP and OS. The combination treatment was shown to be harmful in HCC patients with portal vein invasion. The degree of portal vein invasion may have an impact on survival. Additionally, the favorable OS of combination therapy in patients with a poorer baseline status might be attributed to the convergence of systemic and loco-regional therapies. Some other research found that age was not a determinant of therapeutic response in advanced HCC patients when comparing the combined effectiveness of elderly and non-elderly people.

TACE is a well-known low-risk technique with a low mortality rate that has been steadily decreasing throughout the last twenty years (reportedly 10% in 1991, 1.1% in 1999, and 0.5% in 2006). Hepatic failure (40.1%), cancer mortality (18.2%), and HCC rupture were the major cause of mortality in the TACE research with the largest sample size. There appears to be no agreement on whether or not patients should have TACE sessions repeated. TACE is repeated at defined intervals in some centers, ranging between 2-3 months. We repeated TACE sessions four weeks following treatment based on the findings of a follow-up CT. This policy was comparable to that used in Takayasu et al.’s state-wide’s multicentric Japanese investigation. TACE is said to be more effective when repeated based on follow-up imaging data rather than at predefined intervals.

Conclusions
To conclude, TACE is a pain-relieving method that is both safe and effective. At the time of diagnosis, the patients usually had aggressive cancers. TACE has provided advantageous results, with survival rates comparable to those described by other investigators. In hepatocellular carcinoma individuals, the initial tumor size was the most influential independent predictive factor.

Conflicts of Interest
The author declares that he has no conflicts of interest.

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Ethical Approval
Not applicable.

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