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Role of TACE in Patients with Hepatocellular Carcinoma before Liver Transplantation

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Abstract Transarterial chemoembolization (TACE) can prevent tumor progression in patients with hepatocellular carcinoma awaiting liver transplantation. This article introduces the effect of TACE before liver transplantation in terms of dropout rate, improvement in overall survival, prediction of survival, and its application as down-stage therapy.

Keywords: *hepatocellular carcinoma; liver transplantation; therapeutic embolization*

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1. Introduction

The Milan Criteria are adopted by many transplantation centers for choosingpatients with hepatocellular carcinoma (HCC) as candidates for liver transplantation (LT). However, candidates for LT tend to wait for long periods because of the disparity between the demand and supply of liver. As the waiting time extends, tumor progression may occur, and such condition results in poor outcomes and a high dropout rate. Thus, numerous transplantation centers use locoregional therapy, especially transarterial chemoembolization (TACE), as bridge therapy and down-stage therapy. TACE has become a prominent and standard palliative treatment option for nonresectable liver metastases from primary colorectal cancer and other primary liver neoplasms. TACE, which is also referred to as hepatic artery chemoembolization and hepatic arterial infusion chemotherapy, is a two-step procedure that involves the selective injection of one or more chemotherapeutic agents and the insertion of embolic material into the feeding arteries of the tumor [1]. This procedure leads to two synergistic effects. The injected emboli restrict the arterial blood supply of the tumor, and the chemotherapeutic agent is delivered directly to the target tissue. TACE can induce tumor necrosis and prevent tumor progression. Nicolini D et al. [2] examined the explanted livers of patients undergoing TACE before LT. In this work, the mean tumor necrosis was 52.2% ± 40.9% in the TACE groups, and the superselective procedures increased the percentage of necrosis relative to the non-superselective procedures (73.9% ± 34.3% vs. 31.3% ± 37.0%), respectively. Although TACE can induce tumor necrosis, the effect of TACE before LT remains unclear. This article reviews recent studies on TACE before LT.

2. Effect of TACE on Dropout Rate

Dropout is cruel for patients waiting for LT. The long waiting time results in a high risk of dropout. Alessandro Cucchetti et al. reported 3-, 6-, and 12-month dropout rates at 3.5%, 6.5%, and 19.9%, respectively [3]. Maurizio Pompili et al. also suggested that for patients meeting the Milan criteria, being on the waiting list for more than 6–12 months is a known risk factor of dropout. However, because of the shortage of liver supply, the mean waiting time for donor LT is about 10 months [4]. To reduce the dropout rate, practitioners suggest bridge therapy for patients in the waiting list. Sang-Jae Park et al. [5] reported that a score of >15 in a laboratory model for end-stage liver disease or the presence of multiple tumors at the time of UNOS listing is a significant risk factor for waitlist dropout. Loco-regional therapy can reduce waitlist dropout in patients with HCC awaiting LT, and TACE is the most commonly used neo-adjuvant therapy [6]. A retrospective study presented sufficient evidence to conclude that TACE reduces the rate of dropout from the waiting list [7]. The stratification of candidates in the tumor stage and their response to bridge therapy showed that patients with T2 tumors who achieved only a partial response or no response to bridge therapy recorded the highest dropout rates. The second highest dropout rates were found among the patients with successfully down-staged T3–T4a tumors, followed by patients with T2 tumors who exhibited a complete response and patients with T1 tumors; the latter two groups recorded similar dropout rates. Two large-scale studies confirmed a significantly reduced dropout probability among T2 patients with a complete or partial response to bridge therapy and among patients with an inadequate or no response to treatment [3]. Millonig G et al. demonstrated that patients who did not respond to TACE were more

likely to drop out as a result of tumor progression compared with those with complete or partial responses while waiting for LT [8].

Serum AFP has long been used as a diagnosis index for HCC and as a surrogate marker of vascular invasion. In recent studies, patients who did not show reduced AFP levels of ≤ 400 after TACE showed high dropout rates. Only the last pre-transplant AFP value instead of the original value (even if it was originally > 1,000 ng/mL) or the changes in the AFP level independently predicted the dropout rate in such works. In conclusion, TACE followed by OLT can reduce dropout rates in selected patients, especially those who respond to TACE.

3. Effect of TACE on Overall Survival

TACE can induce tumor necrosis and prevent tumor progression; thus, many investigators have explored the effect of TACE followed by LT on overall survival. However, the literature on pre-transplant TACE presents mixed results. A multicenter retrospective case control study in France compared 100 HCC patients who underwent TACE before transplantation and 100 HCC patients transplanted without any prior treatment. The five-year survival (59% in both groups) and five-year disease-free survival (69% vs. 64%) rates were not significantly different [9]. In a study by Bharat et al. [10], 46 HCC patients undergoing various bridging treatments before LT were compared with 46 matched HCC patients transplanted without any treatment. The five-year survival rate was significantly higher in the treated group than in the non-treated group (82% vs. 52%), although the survival advantage was evident only for patients with T2–T4 tumors and not for those with T0–T1 tumors. The five-year disease-free survival rate was also slightly higher in the treated group than in the non-treated group (84% vs. 76%), although this difference was not significant. Moreover, studies that found no difference between treated and untreated patients also reported short waiting times for LT [11]. Several papers also reveal that TACE is associated with low recurrence irrespective of histological response [12]. TACE cannot improve survival after LT, but during extensive waiting periods for OLT, TACE can be used to keep patients with HCC on the waiting list by preventing tumor progression, with such patients showing similar outcomes to those who underwent transplantation immediately [13]. However, other investigators did not show consistent results. Vivanco M et al. even observed opposite outcomes, that is, survival was slightly low among the bridge therapy groups [14]. Therefore, robust data supporting the survival benefits associated with the application of TACE before LT are expected [15].

4. Effect of TACE on Predicting Survival

Tumor stage and waiting time are the most important factors that influence the outcome of patients with HCC after LT. In recent years, a significant amount of data have shown that response to TACE is another factor indicating good outcomes. Millonig G et al. studied 106 patients who underwent TACE before LT and found that the survival rates at one, two, and five years significantly increased in patients with complete or partial response to TACE in comparison with those with no response: 89.1%, 85.1%, and 85.1%; and 88.6%, 77.4%, and 63.9% versus 68.6%, 51.4%, and 51.4%, respectively ($P < 0.05$ for both comparisons). They concluded that the response to TACE might predict long-term survival in patients after OLT and that the characteristics of tumor response to TACE are reliably recognized and allow the identification of suitable patients for transplantation [8,16]. Kun-Ming Chan and Irene Bargellini reached similar results [17,18]. Antoine Bouchard–Fortier also observed that patients with no cancer recurrence showed more complete necrosis compared with their counterparts (48% vs. 0%) [19]. Progression in the TACE group was associated with a significantly poor outcome concerning overall survival [20]. The response to therapy was taken as a potentially effective tool for prioritizing HCC patients for LT and for selecting cases with different risks of tumor recurrence after transplantation was suggested.

5. Effect of TACE as Down-stage Therapy

Although the term “down staging” refers to the reduction of the clinical stage of a disease from any initial stage (e.g., from T2 to T1), down staging in the context of transplantation for HCC is used for strategies allowing the transplantation of patients who at first do not qualify for OLT because their tumors are outside the accepted criteria (T3 or higher). According to presently available data, the successful down-staging rate ranges between 24% and 71% [7]. The proportion of transplanted patients ranges between 10% and 67%, and the average waiting time for LT ranges between 2 and 10.9 months [21]. Additionally, the reported survival rates range from 78.8% to more than 90% and from 54.6% to 93.8% at three and five years, respectively [22]. Chapman WC found that selected patients with stage III/IV HCC can be down staged to Milan criteria with TACE. More important, patients who are successfully down staged and transplanted show excellent midterm disease-free and overall survival rates, similar to patients with stage II HCC [23]. In sum, TACE is an alternative technology to downstage advanced tumor exceeding the Milan criteria and can thus lead to good outcomes.

6. Conclusion

Owing to the absence of prospective randomized studies, no data can provide level 1 evidence that TACE before LT can reduce the rate of dropout from the waiting list as a result of tumor progression and improve post-LT survival. Nevertheless, the role of TACE before LT in predicting survival and as down-stage therapy is convincing.

Competing interests:

All the authors claim no competing interests.

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