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A Decision Analysis Model Identifies the Interval of Efficacy for Transarterial Chemoembolization (TACE) in Cirrhotic Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation

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Abstract

Introduction For liver transplant candidates with hepatocellular carcinoma (HCC), the ability of neoadjuvant transarterial chemoembolization (TACE) to improve outcomes remains unproven. The objective of our study was to determine if there was a specific time interval where neoadjuvant TACE would decrease the number of HCC patients removed from the pretransplant waitlist.

Materials and Methods A decision model was developed to simulate a randomized trial of neoadjuvant treatment with TACE vs. no TACE in 600 virtual patients with HCC and cirrhosis. Transition probabilities for TACE morbidity (1±1%), TACE response rates (30±20%), and disease progression (7±7% per month) were assigned by systematic review of the literature (18 reports). Sensitivity analyses were performed to determine time thresholds where TACE would decrease the number of delisted patients.

Results TACE treatment had statistical benefit at waitlist time breakpoints of 4 and 9 months ($P<0.05$). When waitlist times were less than 4 months, waitlist attrition was similar (20% vs. 34%, $P=0.08$). When waitlist times exceed 9 months, waitlist dropout rates re-equilibrated (33% vs. 46%, $P=0.06$). Review of the current literature determined that only those studies reporting on patients with waitlist times between 4 and 9 months found a benefit to neoadjuvant TACE.

Conclusions This analysis indicates that the benefit of neoadjuvant TACE may be limited to those patients transplanted from 4 to 9 months from first TACE. These data may help transplant programs to tailor TACE treatments based on predicted waitlist times to achieve optimal resource utilization and improved organ allocation efficiency.

Keywords Primary liver cancer · Adjuvant therapy · Outcomes analysis

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Introduction

The ideal treatment for patients with hepatocellular carcinoma (HCC) and cirrhosis is orthotopic liver transplantation (OLT). In current clinical practice, however, imbalance in the availability of matched donor organs mandates that most of the patients with HCC and cirrhosis will spend a variable amount of time on a waitlist before OLT. During this volatile waitlist period, HCC patients can experience progression of malignant disease and/or complications of cirrhosis, which may reduce or even remove the indication for liver transplantation.

To address the possibility of malignant disease progression while on the waitlist, many transplant programs have offered (and continue to offer) local treatment modalities to

HCC patients, including resection, ablation, and transarterial chemoembolisation (TACE). As TACE appears to have the highest safety margin of these three options, it has become a popular initial treatment modality for patients with HCC awaiting OLT.

Although palliative TACE has been shown to prolong survivals in patients with unresectable HCC who are not transplant candidates,[1] data on the efficacy of TACE as a neoadjuvant treatment for HCC patients awaiting OLT is conflicting. Several studies have shown improvement in the transplant waitlist dropout rate after TACE.[2–5] However, other studies have found no impact on this endpoint.[6,7] Despite early promising results from well-designed single center studies,[8–10] no study has proven that neoadjuvant TACE improves post transplant disease-free survivals.[11–15]

The variability in response rates to TACE suggest that there are multiple factors which influence outcome after this treatment. To better understand these factors, we designed a decision analysis model based on a systematic review of the available literature to determine the time thresholds where neoadjuvant TACE is predicted to significantly decrease the number of delisted patients. These data were then compared to previously published outcomes to determine if the conflicting data in the literature could be explained.

Materials and Methods

Using commercially available software (TreeAge Pro Healthcare Edition, TreeAge, Williamstown, MA), a decision analysis model was developed to simulate a randomized trial of neoadjuvant treatment with TACE vs. no TACE in 600 virtual patients (300 in each group) with HCC and cirrhosis awaiting OLT. This sample size allowed for reliable detection of a 10% difference in dropout rates with an alpha of 0.05 and a beta of 0.10. Transition probabilities for decision points were assigned by systematic review of the English language literature (18 relevant reports), including TACE morbidity (1±1%), TACE response rates (30±20%), and progression of malignant disease (7±7% per month). Median waitlist times were varied from 1 to 18 months at 1 month intervals. An assumption was built into the model that TACE treatments would be repeated every 2.5 months up to a maximum of three total treatments. Sensitivity analyses were performed to determine the impact of study factor variance on the time thresholds where TACE would significantly decrease the number of delisted patients. Chi-squared tests were used to assess differences in dropout rates at each waitlist time interval.

The model was validated by comparing the median waitlist times and dropout rates for previously reported clinical studies that found a benefit for TACE before OLT to those studies that found no benefit for neoadjuvant TACE.

Results

Analysis of Decision Model Output

Analysis of the decision model output comparing waitlist dropout rates in virtual patients treated with and without neoadjuvant TACE while varying the waitlist time determined that TACE treatment had statistical benefit at waitlist time breakpoints of 4 and 9 months ($P<0.05$, Fig. 1). When waitlist times were less than 4 months, waitlist attrition was similar (20% vs. 34%, $P=0.08$). When waitlist times exceed 9 months, cumulative morbidity from repeated TACE treatments and disease progression outweighed the benefits of TACE and led to re-equilibration of waitlist dropout rates (33% vs. 46%, $P=0.06$).

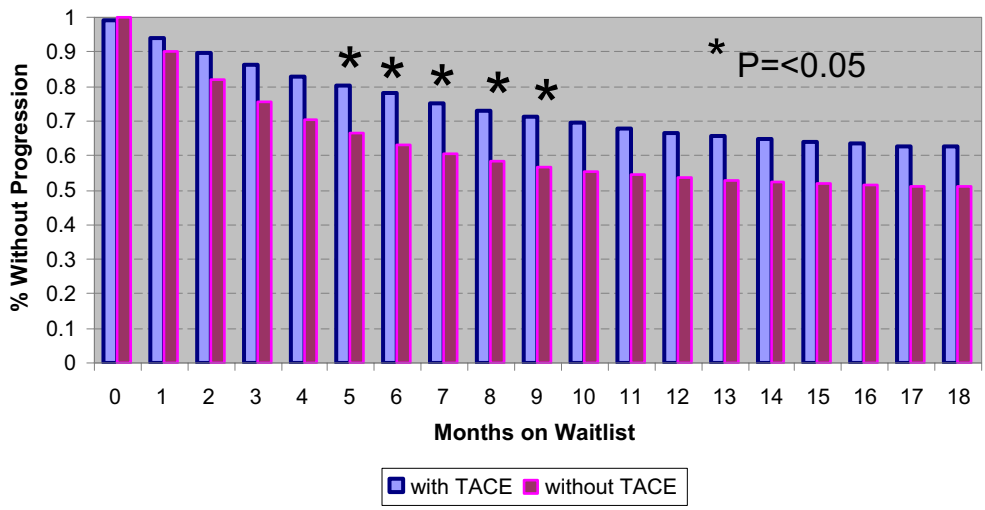

Figure 1 Differences in transplant waitlist dropout because of disease progression between 300 virtual patients treated with neoadjuvant TACE and 300 virtual patients with no TACE treatments before liver transplantation.

Sensitivity Analyses

To determine the impact on differences in waitlist dropout rates and significant waitlist time intervals, sensitivity analyses were performed for each study variable. Variance of the disease progression rate had no impact on the waitlist time interval. Likewise, variance of the TACE complication rate had no influence on the waitlist time interval. In contrast, variance of the TACE response rate did impact the duration of the significant time interval. When the TACE response rate was greater than 50%, the waitlist time interval where differences in the waitlist dropout rates remained statistically significant was extended from 4 to 11 months after initial TACE treatment.

Validation of the Decision Model

The six studies (all single center), which report waitlist dropout rates for patients undergoing TACE while awaiting liver transplantation, were examined to determine the median number of TACE treatments delivered, the waitlist dropout rate, and the median times to dropout or transplant (Table 1).[2–7] Four of the six studies were positive, concluding that TACE was associated with reduced waitlist dropout (range 0–18%) and a benefit to patients awaiting liver transplant.[2–5] In contrast, the remaining two studies were negative, concluding that TACE had no impact on waitlist dropout (range 35–46%).[6,7] The median time to liver transplant for each of these studies was plotted (Fig. 2). This plot reveals that each of the positive studies were from programs with median waitlist times between 4 and 9 months. All of the studies reporting negative results were from programs with a median waitlist time ≤4 or >9 months.

In addition, studies comparing long-term post OLT outcomes (disease-free and overall survivals) in patients treated with and without neoadjuvant TACE were examined (Table 2). Three of these studies include data on waitlist times.[12,15,16] Both Oldhafer et al. and Decaens et al. reported on patients with short waitlist times (range 118–128 days) and found no impact of neoadjuvant TACE on survivals. The third study, by Porrett et al., reporting data on waitlist times, bridges the MELD scoring era. In the preMELD era, the median waitlist time was 574 days and in the postMELD era, the median waitlist time was 54 days. As predicted by the decision analysis model, neither cohort reported in this study was found to have a survival benefit from TACE (13 of 31 treatment group patients in this study received TACE).

Discussion

A recent systematic literature review has concluded that TACE has no benefit in patients awaiting liver transplantation.[17] This conclusion is contrary to the experience at many transplant centers, which continue to use TACE as a primary therapeutic modality in patients with HCC and cirrhosis. To resolve these discrepancies, we developed a decision analysis model that took the form of a randomized trial comparing TACE treatment to no TACE treatment with 300 virtual patients in each arm. The aim of the study was to identify a time threshold where TACE would have the greatest benefit. Furthermore, we validated the model's findings by analyzing reported waitlist dropout rates in negative and positive TACE studies.

The significant finding from the analysis of the decision model was that TACE was predicted to only benefit patients

Table 1 Studies assessing the impact of neoadjuvant TACE on waitlist dropout rates

Author, year	No of patients	Stage	Mean waitlist time (OLT/dropout)	Dropout (%)	Factors associated with dropout
Roayaie et al., 2002[7]	80	III, IV	142 d/207 d	46	Tumor size
Graziadei et al., 2003[2]	48	I, II	178 d/–	0	–
	15	III, IV (downstaged)	254 d/189 d	20	Stage IVa
Hayashi et al., 2004[6]	20	I, II	343 d/na	35	None
Maddala et al., 2004[5]	54	I, II	211 d/83 d	15	None
Fisher et al., 2004[4]	22	I, II, III	276 d[a]/225 d	18	AFP>400 ng/ml T-stage=3 Bilobar HCC
Yao et al., 2003[3]	58	I–II	180 d/280 d	11	Tumor no >2
		I–III	186 d/323 d	31	Solitary HCC>3 cm Lack of NAT

No number, *d* days, *NAT* neoadjuvant treatment, *na* not available.
[a] PreMELD mean waitlist time 410 days, PostMELD mean waitlist time 66 days.

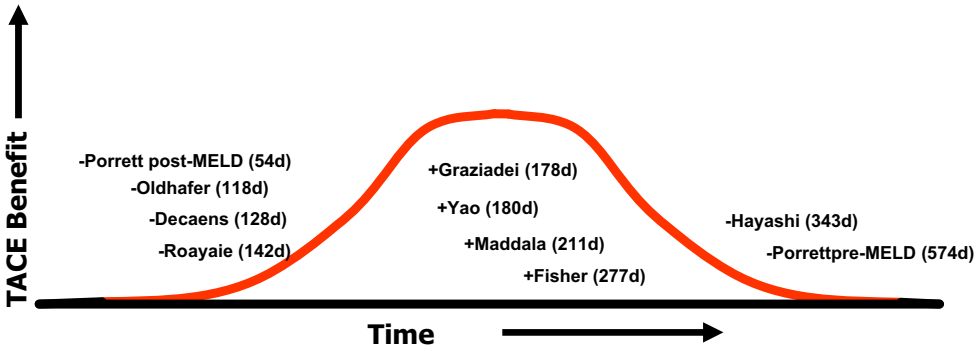

Figure 2 Plot of positive (+) and negative (−) studies for neoadjuvant TACE in transplant waitlisted patients comparing average waitlist times to the predicted interval of peak TACE efficacy.

with HCC who were transplanted between 4 and 9 months from initiation of TACE treatments. This finding was supported by the six available reports on this topic. All clinical studies that found a benefit to neoadjuvant TACE reported median waitlist times from 178 to 277 days.[2–5] In contrast, the remaining studies, which found no benefit to TACE, were all from centers with median waitlist times ≤4 or >9 months.[6,7] Furthermore, three studies, which report no benefit to neoadjuvant TACE in terms of long-term outcomes, were also found to have median waitlist times ≤4 or >9 months.[12,15,16]

Several studies have shown that, after various local treatments, dropout increases with time on the transplant waitlist.[3,18,19] It is interesting to note that Yao et al. have demonstrated that the highest frequency of dropout occurs between 6 and 12 months on the waitlist.[3] In 58 patients who initially met the UNOS transplant criteria, they found that the cumulative waitlist dropout rate at 6 months was 11%, rising steeply to 57% at 12 months, and plateauing thereafter, with a cumulative 24-month dropout rate of 75%. These findings suggest that local therapies that reduce disease progression during this time interval of peak waitlist dropout could significantly impact outcomes for waitlisted patients.

Conclusion

We conclude from these analyses that the question of whether or not TACE is beneficial to patients with HCC who are awaiting liver transplantation does not have an absolute yes or no answer. TACE is likely to benefit certain patients, specifically those with a predicted waitlist time from 4 to 9 months. Given these findings, individual centers should be able to tailor the use of TACE therapy based on historical waitlist times, blood group, HCC stage, severity of cirrhosis, and waitlist rank (i.e. MELD score). This approach would be anticipated to maximize TACE

Table 2 Recent studies comparing outcomes for patients with hepatocellular carcinoma treated with neoadjuvant TACE and untreated before liver transplant

Author	Year	No of pts treated/untreated	Stage	Waitlist time	Dropout	Survivals (year)		
						1	3	5
Majno et al.[13a]	1997	54	na	na	na	74%	62%	57%
		57	na	na	na	77%	66%	59%
Oldhafer et al.[12]	1998	21	I–IV	118d	na	61%	48%	na
		21	I–IV	na	na	62%	54%	na
Perez Saborido et al.[20]	2005	18	I–IVa	na	na	83%	61%	61%
		28	I–IVa	na	na	77%	59%	38%
Decaens et al.[15]	2005	100	I–IV	128 d	na	na	na	59%
		100	I–IV	131 d	na	na	na	59%
Yao et al.[21a]	2005	85	T2/3	na	na	96%	na	94%
		41	T2/3	na	na	92%	na	81%
Porrett et al.[16]	2006	31[b]	T1–2	574 d/54 d[c]	na	na	84%	na
		33	T1–2	543 d/199 d[c]	na	na	91%	na

No number, *pts* patients, *d* days, *na* not available.
[a] Survivals are disease/recurrence-free.
[b] Only 13 patients were treated with TACE.
[c] Waitlist times preMELD/postMELD.

benefit, reduce exposure to TACE related morbidity, reduce unnecessary resource utilization, and improve organ allocation efficiency.

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