TECHNICAL NOTE

TILA-TACE – an approach for effective local control of hepatocellular carcinoma

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INTRODUCTION

HCC is the sixth common cancer but the third leading cause of cancer-related death (1). More than 50% of all HCC patients worldwide are from China alone. The incidence rate of HCC is nearly equal to the mortality rate(1), indicating a highly unmet medical need. Most HCC patients at first diagnosis are already at the BCLC (Barcelona Clinic Liver Cancer Staging Classification) stage B or C, not suitable for curative therapy including surgery, ablation, and liver transplantation. The option is TACE (2-4).

The purpose of TACE is for loco-regional control of HCC instead of systematic treatment of the disease. TACE kills HCC mainly via 2 mechanisms, (1) injecting concentrated chemotherapeutic agents directly into tumor feeding arteries to exert a cytotoxic effect on tumor, followed by (2) blocking the arteries to cut off the nutrient supply to starve cancer cells. Some interesting studies demonstrated that transarterial embolization achieved a tumor response rate comparable to TACE (5, 6), indicating that cutting off the nutrient supply played a major role.

The objective tumor response to cTACE is 35% (range, 16% to 61%, multiple courses of TACE treatment)(7). The complete tumor response to cTACE is rare (0-4.8%) (8). A major obstacle to limit the therapeutic efficacy of cTACE is the size of HCC, as the therapeutic efficacy is inversely correlated with the size of tumor. In our 30-year clinical practice of cTACE, the most frequently seen response of large tumors to cTACE is shown in Figure 1-3: a patient had a huge HCC at right lobe (Figure 1), although the operation was technically sound (Figure 2), the treatment outcome was far from satisfaction, leaving a large portion of viable residues crisscrossed in the treated tumor (Figure 3). The tumor was eventually out of control and grew progressively (Figure 4). Taken together, cTACE has reached its therapeutic limit. Therefore, unless a new principle is implemented into cTACE, its therapeutic efficacy would not be significantly improved.

MECHANISMS THAT LIMIT THE THERAPEUTIC EFFICACY OF CTACE

The therapeutic efficacy of cTACE is mainly determined by embolization of tumor feeding arteries, which provide essential nutrients, such as oxygen, glucose, amino acids. If the embolization is truly complete and thorough, tumor would inevitably, unconditionally, and rapidly die without question, because thorough embolization would quickly terminate all the biochemical reactions that support tumor cell survival/proliferation.

Biochemical reactions are the basis for both normal and cancer cells to survive and to proliferate. Although the network of biochemical reactions is a complex theme, we could simplify them into electron flows that link initial electron donors to ultimate electron acceptors. Oxygen is the ultimate electron acceptor in biochemical reactions in living cells. Thorough deprivation of oxygen would result in termination of electron flows, so that all biochemical reactions could not proceed in order and the whole network of biochemical pathways would stop working properly, leading cells to death.

Although thorough embolization of tumor is the aim, it is unlikely in practice. Even if all the tumor feeding arteries are identified and blocked, the embolized tumor may acquire essential nutrients such as oxygen and glucose from other sources, e.g., from adjacent normal tissues, as a nutrient gradient exists, higher in normal tissues and lower in tumor tissues, and it drives nutrients diffuse from normal tissues down to tumor tissues. Therefore, tumor tissues may obtain essential nutrients, which, although not in quantity, may satisfy the least demands of biochemical activities, preventing cancer cells from reaching metabolic death threshold, so that a fraction of cancer cells in the embolized tumor may survive.

TACE can achieve a partial embolization of the targeted tumor and create a stress condition. Although the stress kills quantity of cancer cells, it spares a fraction of them owing to the following reasons: 1) although oxygen level drops markedly, it is not deprived, and low oxygen level may support a basal level of electron flow to maintain the orderly biodegradation and biosynthesis; 2) glucose remained in the tumor or diffused from the adjacent normal tissues may support survival of cancer cells; and 3) cTACE creates a hypoxic condition, a strong inducer to stimulate cancer cells to mobilize angiogenesis (4), eventually revascularizing the embolized tumor, which then grows progressively.

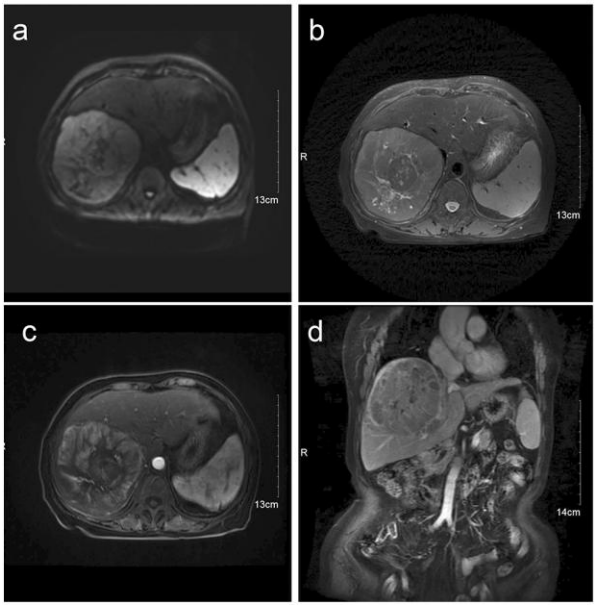

Figure 1. Patient A receiving cTACE treatment. Contrast-enhanced MRI images of a huge hepatocellular carcinoma (13.5 cm) in the right lobe before the first session of treatment. (a)DWI. (b)T2WI. (c) Axial, TIWI with contrast-enhanced MRI, arterial phase. (d) Coronal, TIWI with contrast-enhanced MRI, arterial phase.

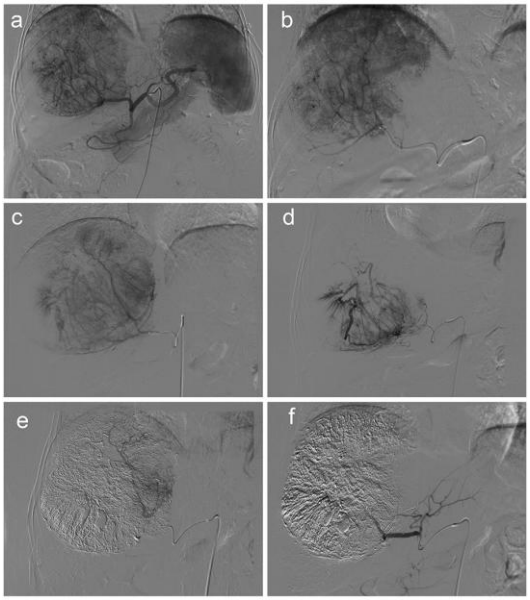

Figure 2. Patient A receiving cTACE treatment. DSA angiography during the first session of treatment. (a) Celiac artery angiography before embolization. (b-e) Superselective angiography of tumor feeding arteries. (f) Celiac artery angiography after embolization, tumor staining disappeared.

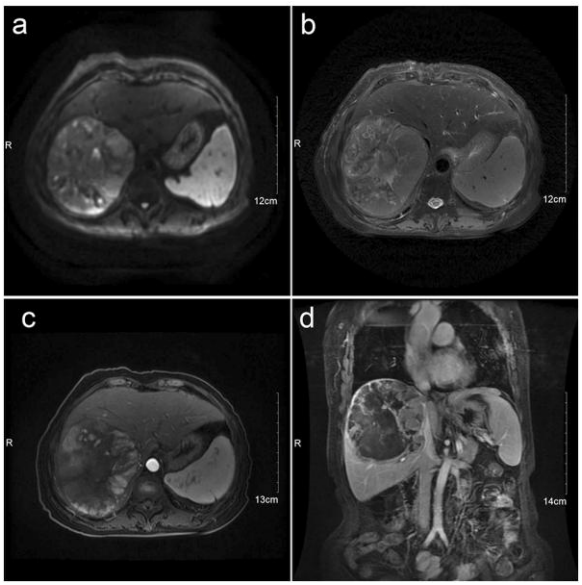

Figure 3. Patient A receiving cTACE treatment. The outcome of the first session of treatment. Forty days after treatment, tumor necrosis was examined by liver contrast-enhanced MRI. (a) DWI. (b) T2WI. (c) Axial, TIWI with contrast-enhanced MRI, arterial phase. (d) Coronal, TIWI with contrast-enhanced MRI, arterial phase.

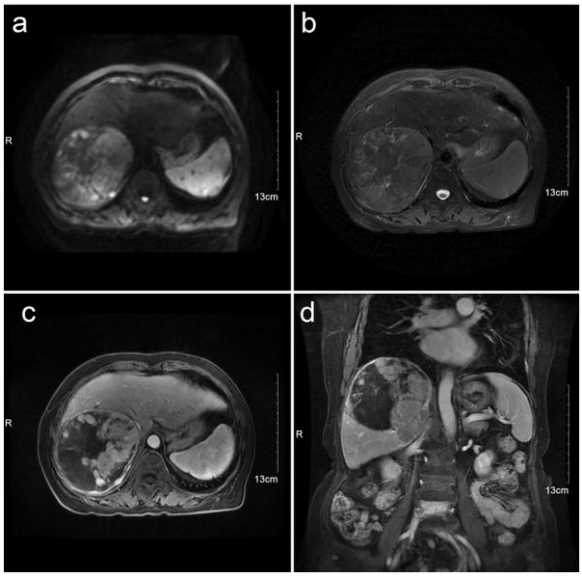

Figure 4. Patient A receiving cTACE treatment. Liver contrast-enhanced MRI images 4 months after the second session of cTACE, showing the progressive growth of the tumor.

GLUCOSE DEPRIVATION IS A KEY TO BREAK THE THERAPEUTIC BOTTLENECK OF TACE

The rationale as described above provides a clue to break therapeutic limit of TACE. TACE creates a harsh condition of low oxygen and glucose levels, which can only support cancer cells to survive for a limited period of time. If the embolized tumor could not revascularize itself, it would die. Thus, the key point is to kill the tumor before it reestablishes circulation.

In living cells, while oxygen is the final electron acceptor, glucose is a major electron donor. The electron flow from glucose to oxygen occupies a central position in maintaining cellular redox and energetic homeostasis. In addition, the metabolic intermediates of glucose are used for biosynthesis, e.g., ribose-5-phosphate is essential for RNA and DNA synthesis. Therefore, glucose is metabolically indispensible for cells, especially for proliferating cancer cells. Other nutrients, such as amino acids, fatty acids, cannot fully compensate for glucose shortage. They can serve as energy sources, but cannot be converted to ribose-5-phosphate, which is essential for RNA and DNA metabolism. Thus, in principle, depriving glucose is an effective way to kill cancer cells.

One may ask if glucose can fully compensate for amino acid metabolism and the answer is no. Then, why only lay stress on glucose? The plausible explanation is that amino acids are abundant in tumor tissues(9). Even if blood supply is cut off, cancer cells could recycle components of dead cells to amino acids and fatty acids, whereas glucose can be only supplied by blood circulation.

RESISTANCE OF CANCER CELLS TO GLUCOSE DEPRIVATION

TACE blocks tumor feeding arteries thus blocks the highway of glucose and oxygen supply. The amount of glucose in the embolized tumor is limited and the low oxygen level speeds up glycolysis, leading to a quick exhaustion of glucose. Theoretically, exhaustion of glucose should effectively kill cancer cells, but practically, most tumors can survive through embolization (8) , suggesting that some unidentified factors exist in tumor environment that can help cancer cells resist glucose deprivation.

RESISTANCE OF CANCER CELLS IN SOLID TUMORS TO GLUCOSE DEPRIVATION

It has long been known that tumor vasculature is both structurally disorganized and functionally inefficient, resulting in a poor exchange of substances between blood and tumor tissue. As summarized by Bergers and Benjamin(10): tumor blood vessels are irregularly shaped, dilated, tortuous, even can have dead end; vessels are integrated with tumor cells; vessel network is not organized into definitive venules, arterioles and capillaries; vessel network is leaky and hemorrhagic; blood flow is slow and even can oscillate, and among others.

Accordingly, glucose level in solid tumors is very low, e.g., 0.1 and 0.4 mM in stomach and colon cancer biopsies, respectively, in contrast to average 5.5 mM blood glucose(9). Interestingly, the other nutrients such as amino acids are abundant(9), probably suggesting that amino acids could be metabolically recycled (e.g., through autophagy or through “eating” dead cells) in tumor tissues in addition to blood circulation, whereas glucose could not be metabolically recycled and can be only supplied by blood circulation. Furthermore, temporal and even constant glucose deprivation in solid tumors is common(10-12). All the lines of evidence suggested that cancer cells in the poorly vascularized tumor can resist glucose deprivation. As cancer cells alone cannot resist glucose deprivation, there must be some environmental factors that help cancer cells resist it.

LACTATE AND PROTON ENABLE CANCER CELLS TO RESIST GLUCOSE DEPRIVATION

Cancer cells consume glucose wastefully, termed Warburg effect, named after Otto Warburg, who discovered this metabolic phenotype of cancer cells(13). Cancer cells have an exceptionally large capacity to consume glucose(14-18), converting most incoming glucose carbon to lactate, even in the presence of ample oxygen, e.g., if 4T1 cells were cultured with a sufficient supply of glucose and other nutrients, as estimated, <1 mg 4T1 cell mass would reach >1000 tons in 22 days, by consuming >3000 tons of glucose and generating > 2000 tons of lactate(19). Such a capacity of cancer cells to use glucose jeopardizes themselves to the risk of glucose deprivation, as in vivo, tumor glucose supply is both physiologically and physically confined and in fact is far from sufficiency. Therefore, in order for a tumor to survive and to grow, cancer cells must constantly adjust glycolysis rate to balance glucose supply and consumption.

In many solid tumors, lactate and proton accumulate, creating a chemical environment called lactic acidosis (high lactate concentration with acidic pH), possibly as a result of glycolysis and glutaminolysis. In our previous report, lactate and proton played critical roles in regulating cancer cell glycolysis(20-22). Cytosolic proton and lactate synergistically regulate glycolysis and the metabolic fate of glucose. Proton inhibits glycolytic enzymes leading to a reduced glycolytic flux, lactate concentration is the major one to dictate the mass action ratio of the lactate dehydrogenase (LDH)-catalyzed reaction. When the mass action ratio is equal to the equilibrium constant, the equal forward and backward rates of the LDH-catalyzed reaction allow pyruvate generated from glycolysis flow to metabolic pathways (e.g., pyruvate carboxylation, Krebs cycles, etc.) other than to lactate. When condition changes either way, there would be a

positive or negative net lactate production. Conceivably, lactate and proton may play a critical role in regulating glycolysis rate to balance glucose supply and consumption in solid tumors.

When glucose is used up, lactate and proton together can rescue cancer cells from glucose deprivation-induced death, through 1) arresting cancer cells at G0/G1 phase of cell cycles, a metabolically least demanded state, 2) activating moderate autophagy to recycle cellular components, and 3) inhibiting apoptosis to reduce cell death rate (20).

It is important to point out that it is proton and lactate together that confer cancer cells with ability to use glucose in a highly economical and efficient way and to resist glucose deprivation, not lactate nor proton alone(20-22).

PROPOSED STRATEGY TO TREAT CANCER BY DISRUPTING THE SYNERGISM OF LACTATE AND PROTON

The revelation of synergistic effect of lactate and proton on cancer cells' glucose metabolism may deliver a novel strategy to treat cancer. The hypothetical approach to treat cancer is to converting lactic acidosis to lactosis, by injecting or infusing a base, e.g., bicarbonate, into tumor bed. We provided evidence that this approach worked in vitro and in vivo (20, 21, 23).

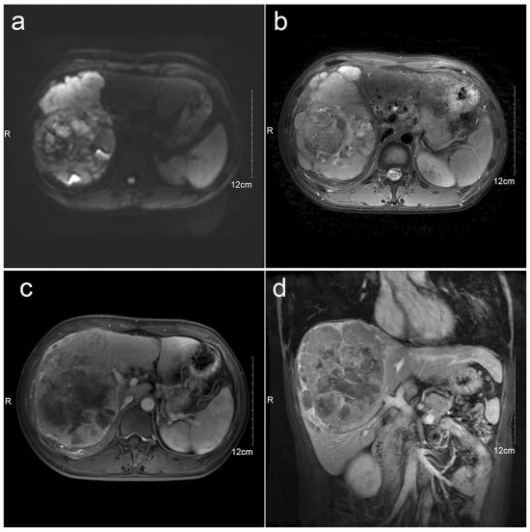

Figure 5. Patient B treated with TILA-TACE. Contrast-enhanced MRI images of a huge hepatocellular carcinoma (19.6 cm) in the right lobe before the first session of treatment. Huge hepatocellular carcinoma in the right lobe with rich vascular supply. (a) DWI. (b) T2WI. (c) Axial, TIWI with contrast-enhanced MRI, arterial phase. (d) Coronal, TIWI with contrast-enhanced MRI, arterial phase.

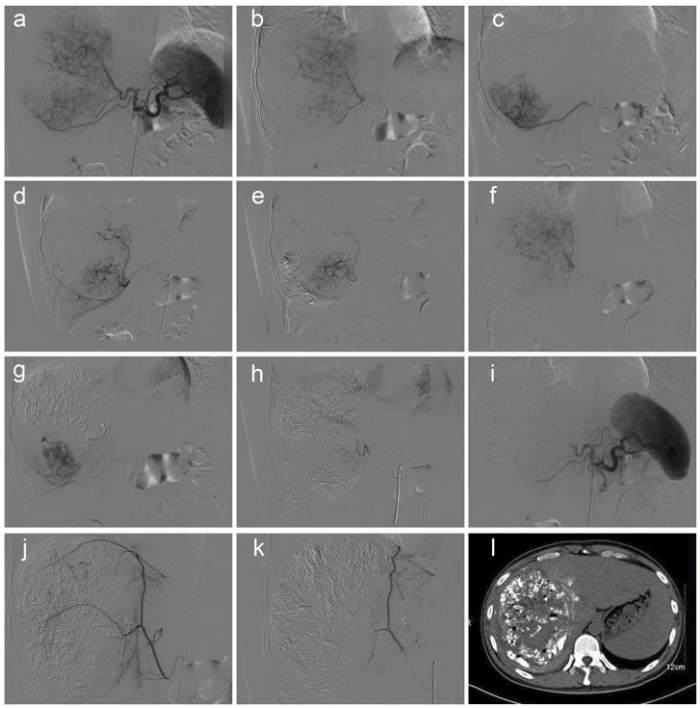

Figure 6. Patient B treated with TILA-TACE. DSA angiography during the first session of treatment. (a) Celiac artery angiography before embolization. (b-g) Superselective angiography of tumor feeding arteries. (h) Proper hepatic artery angiography after embolization, tumor staining disappeared. (I) Right inferior phrenic artery angiography before embolization. (J) Celiac artery angiography after embolization. (K) Right inferior phrenic artery angiography after embolization. (l) Liver plain CT 3 days after first session of TILA-TACE, showing lipidol oil deposition in the lesion.

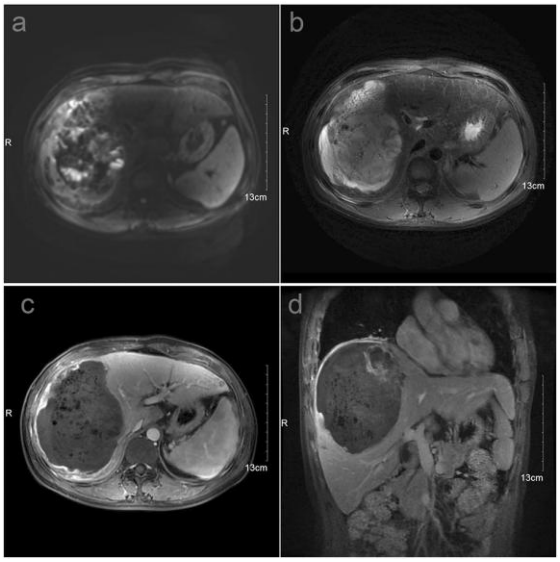

Figure 7. Patient B treated with TILA-TACE. The outcome of the first session of treatment. Twenty days after treatment, the patient was scanned with MRI, which demonstrated a near complete necrosis of the tumor. (a) DWI. (b) T2WI. (c) Axial, TIWI with contrast-enhanced MRI, arterial phase. (d) Coronal, TIWI with contrast-enhanced MRI, arterial phase.

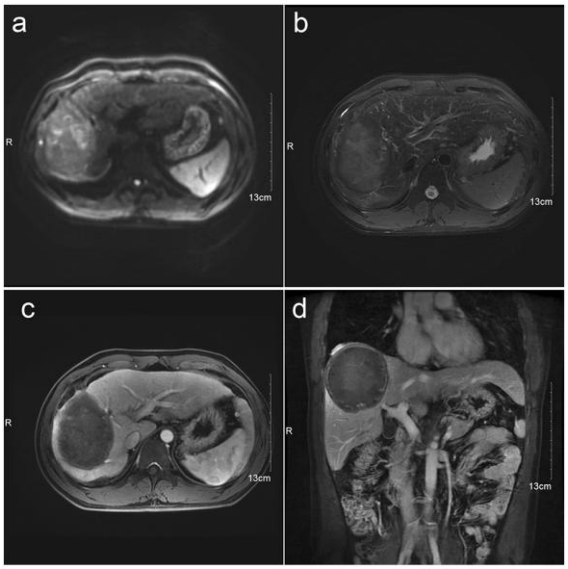

Figure 8. Patient B treated with TILA-TACE. Liver contrast-enhanced MRI images 20 months after the second session of treatment show a stable complete necrosis of the treated tumor. (a) DWI. (b) T2WI. (c) Axial, TIWI with contrast-enhanced MRI, arterial phase. (d) Coronal, TIWI with contrast-enhanced MRI, arterial phase.

TILA-TACE

Although TACE blocks nutrient supply, it also traps lactic acidosis in the embolized tumor. Lactic acidosis reduces glycolysis rate and enables cancer cells to use glucose in a highly economical and efficient manner (21) and to survive for a much longer time than without lactic acidosis even after glucose is used up (20). Moreover, the hypoxia is a potent inducer that triggers cancer cells to initiate angiogenesis. If the above proposed hypothesis works, disrupting synergistic effect of lactate and proton will expose the weakness of cancer cells' dependence on glucose. We then designed TILA-TACE(24), using bicarbonate to neutralize tumor bed, converting intratumoral lactic acidosis to lactosis. TILA-TACE demonstrated a superior activity in local control of large and huge tumors (24). Figure 2 demonstrated frequently seen outcome after first session of TILA-TACE treatment (Figure 5-7). The first-round treatment achieved a massive and clean death in the embolized area, leaving only minimal residues, which was eliminated by the second-round treatment (Figure 8). The markedly improvement of local HCC control correlated with an extended survival of patients(24).

PERSPECTIVES

The ultimate purpose of cancer research is to improve the life quality and to extend the survival of cancer patients. TILA-TACE demonstrated a superior therapeutic efficacy toward large and massive HCC, which could not be effectively treated by other means. Our unpublished data indicated that patients with complete control of large or huge HCC showed a remarkably longer survival than those with partial control of HCC, and the earlier the complete control of HCC, the longer the survival. Thus, the therapeutic aim in the future is to achieve complete response as quickly as possible, in order to significantly improve the life quality and survival of HCC patients.

TILA-TACE is based on a biochemical principle of glucose metabolism of cancer cells. The principle may also help to treat other types of cancers.

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