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Will cancer cells be defeated by sodium bicarbonate?

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Chao et al. reported an improved version of the transarterial chemoembolization (TACE) procedure for large hepatocellular carcinoma (HCC), in which 5% sodium bicarbonate was infused into tumors to supplement chemotherapeutic agents. In a small randomized control trial, TACE combined with bicarbonate yielded a 100% objective response rate (ORR), a significant improvement from the 63.6% ORR in the TACE alone group (Chao et al., 2016).

This optimized procedure is termed targeting-intratumoral-lactic-acidosis TACE (TILA-TACE), as the authors expect sodium bicarbonate to interrupt lactic acidosis of tumors. Previously, *in vitro* studies from the same group suggested that lactic acidosis could effectively protect cancer cells against glucose starvation or deprivation (Wu et al., 2012). The phenomenon of lactic acidosis is characterized with an increase in acidity (acidosis) and a buildup of lactate (lactosis). By directly injecting sodium bicarbonate into tumors, the TILA-TACE procedure is expected not to change the lactate concentration in the tumor microenvironment, but to increase the pH to ameliorate acidosis. Thus, the procedure should be considered as an interruption for acidosis instead of lactic acidosis. However, the *in vitro* study suggested that acidosis alone, but not lactosis, significantly prolonged the survival time of cancer cells under glucose deprivation (Wu et al., 2012). Since the acidosis is more critical for the survival of tumor cells, it would not be a surprise to see a dramatic effect on tumor apoptosis by simply modulating the pH of the tumor microenvironment with sodium bicarbonate.

THE LIMITATION OF TILA-TACE

As pointed out by Chao and his colleagues, the TILA-TACE procedure is developed as an alternative for TACE, which is for large localized HCC, and it will not be helpful for metastasized tumors. The addition of sodium bicarbonate to the procedure has greatly improved ORR, from 44% in non-randomized trials and 66% in randomized trials to 100% (Chao et al., 2016). Historically the average ORR for TACE is 35%, and is similar to the ORR observed in the TACE control group. While the complete tumor response to TACE is expected to be less than 5%, 23%–30% were reported for TILA-TACE. When viable tumor residues (VTR) after treatments were compared, TILA-TACE was shown to further reduce the VTR by about 80% in both non-randomized and randomized trials.

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Unfortunately, the enthusiasm started to fade after the overall survival data were inspected. Due to the small size of the randomized trial and the cross-over patients from TILA to TILA-TACE, no overall survival advantage was observed for the TILA-TACE treatment. However, the results from nonrandomized cohort showed a 3-year survival of 25.9% (95% CI 11.5%–43.1%) for TACE and 61.8% (95% CI 39.7%–77.8%) for TILA-TACE, indicating a survival benefit is likely achieved with the improved procedure. Considering the minimum additional cost for TACE to include bicarbonate, any survival benefit that extends the life of patients for months or even weeks should be undoubtedly appreciated. However, TILA-TACE is far from a cure for cancers.

With the 100% ORR results highlighted in many headlines, the clinical benefit of TILA-TACE was amplified by the news media. In China, there were patients' requests to oncologists for sodium bicarbonate injections, regardless of the cancer types and stages of the patient. Unfortunately, many people exposed to the news were unaware of that patients in TILA-TACE trials also received chemotherapeutic agents. There was even a rumor that a clinical trial with bicarbonate alone would be planned to confirm the efficacy for this economic and "magic" cancer therapy. Although the longing of cancer patients for an affordable and potent cancer treatment is understandable, the high hope for bicarbonate alone as a cancer treatment is without any scientific basis. Giving it to patients as a standalone cancer treatment would be unethical, as this might only cost HCC patients their opportunity to be treated effectively as early as possible.

One question is why the 100% ORR failed to translate into a robust survival benefit? The object response in the TILA-TACE trials was calculated by the measurement of viable tumor residues at 30 days after the treatment. This is a common practice following the EASL criteria, but not an ideal prediction for the recurrence. For example, if the viable tumor residue in a patient is reduced to 10% after the treatment, it will be characterized as CR. However, the 10% of cancer cells may quickly expand within a short period time and the patient will need to have another treatment. This is similar to the situation in surgery for local lesions when margins are positive for tumor cells. In addition, cancer cells survived TILA-TACE might be more malignant and the recurrence could occur quickly.

CANCER CELLS AND THE WARBURG EFFECT

Cancer cells have a specific metabolism known as the Warburg effect, which refers to the high rate of glycolysis followed by lactic acid fermentation in the cytosol to produce energy to supply proliferation. This is in contrast to the low rate of glycolysis in most normal cells followed by oxidation of pyruvate in mitochondria (Figure 1). This unique glycolysis in cancer cells not only provides a way for quickly obtaining energy, but may also contribute to the escape of tumor cells from immune surveillance due to the enhanced immune suppression by lactate (Marchiq and Pouyssegur, 2016).

A variety of therapeutic approaches have been developed against this pathway (Ganapathy-Kanniappan and Geschwind, 2013). However, as almost all of these targets also play roles in normal cells, toxicity of glycolysis inhibitors is always a concern, even though some targets are selectively overexpressed in tumors. For example, lonidamine, a dechlorinate derivative

of indazole-3-carboxylic acid, is an inhibitor for the enzyme HKII that is responsible for the first step of glycolysis. This compound was studied in clinical trials in 1980–1990. In one trial, response to lonidamine was observed in five patients, but treatment was discontinued in seven patients due to toxicity (Band et al., 1986). Lonidamine was later tested in combination with other chemotherapeutic agents, but it is not currently under any active clinical development due to the lack of significant benefit.

It should be noted that lactic acidosis does occur in cancer patients, and in patients with severe conditions, an intervention is required. In fact, sodium bicarbonate infusion is the primary medical measure for correcting the acidity of lactic acidosis. In addition, for patients who have lactic acidosis and fail on sodium bicarbonate, Dichloroacetic acid (DCA, an inhibitor of pyruvate dehydrogenase kinase 2, PDK2) is used. By inhibiting PDK2, DCA promotes the entry of pyruvate into TCA and thus reduces lactic acid formation. However, none of these agents are considered as a cure for cancers. In fact, DCA is known as a carcinogen, at least in animals (DeAngelo et al., 1991).

CD147 is a receptor overexpressed on liver cancer and can interact with MCT1/MCT4, the transporters for lactate in and out of tumor cells. A radiolabelled therapeutic antibody against CD147 (metuximab) has been tested in clinical trials in China. In combination with TACE, metuximab significantly improved the survival of advanced HCC patients in a non-randomized control trial (He et al., 2013). If the survival benefit of TILA-TACE is further confirmed by additional trials and becomes a routine practice, the expensive antibody-based therapy will have a hard time to compete TILA-TACE for local and intermediate stage HCC, but it may have utility for extrahepatic spread in the advance stage of HCC.

DIETARY EFFORTS TO AID CANCER TREATMENTS

While the development of therapeutics targeting specific glycolysis is challenging and has not yielded any approved therapy, there are some dietary theories for manipulating glucose metabolism. The ketogenic diet (KD) is a high fat and low carbohydrate/protein diet that causes the metabolism to shift from glucose to ketones as the primary source of energy. In medicine, KD is used primarily to treat refractory epilepsy in children. Homeopathic believers have adopted KD for cancer management. According to the published results for clinical trials that involve KD, there is no conclusive evidence to support this as a real therapy for cancer yet, although it may be helpful in certain types of cancers, e.g. glioma (Schwartz et al., 2015). In fact, it has only recently been found that immune cells are also dependent on glycolysis to perform immune surveillance for cancer cells, and anything that restricts glycolysis may also impede immune actions against tumors. It is also reported that one function of current immune checkpoint inhibitors is to rescue immune cells from repressed glycolysis (Qorraj et al., 2016).

Clearly, much more effort is needed to develop a smart strategy to target glycolysis for cancer treatments. It is, unfortunately, almost impossible to simply “starve” cancer cells to death. However, it has been reported that short time fasting before chemotherapy can protect leukocytes from therapy- induced DNA damage and may reduce side effects of chemotherapy (Dorff et al., 2016). It is hoped that more simple supplemental treatments or

dietary practices can be developed to facilitate cancer therapies before a real and potent therapeutic glycolysis inhibitor is clinically available.

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Figure 1.

(Color online) Glycolysis in cancer cells. Cancer cells are dependent on glycolysis for energy and produce lactate and protons (H⁺) as metabolites, which are pumped out of cells and create an acidic immune-suppressive tumor microenvironment. By neutralizing H⁺, the sodium bicarbonate in the TILA-TACE procedure was shown to improve the clinical outcomes of TACE.