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Paradigm Shift in Cancer Treatment: Cancer Treatment as a Metabolic Disease – Fusion of Eastern and Western Medicine

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Abstract

Current standard therapies for cancer, including surgery, anti-cancer drugs, and radiotherapy, are thought to contribute to the improvement in the survival rates of cancer patients. However, such standard therapies have 3 major problems: in advanced cancers, it is unlikely that standard cancer treatments will cure the disease; adverse side effects that accompany standard cancer treatments put many patients in distress; and a large amount of medical expenditure is required for new and expensive anti-cancer drugs. These problems may be viewed as a result of establishing treatments without any consideration regarding the root cause of the cancer. Otto Warburg suggested that particular changes in the energy metabolism of cells, which are associated with a shortage of oxygen, are the root cause of cancer. Cancer cells have unique metabolic characteristics, and thus we believe that it is important to treat cancer as a metabolic disease. More specifically, not only is it important to suppress cancer cell metabolism, but it is also important to improve the chronic inflammation that is associated with the

development and progression of cancer, and to support the functions of immune cells. This type of view of cancer treatment coincides with the principles of Chinese medicine, which has a history of 4000 years, such as "*fuzheng quxie*" and "*zhibing qiuben*", which can assist in the establishment of cancer treatments for patients. In this article, we discuss cancer treatments from the view of cancer as a metabolic disease and their association with Chinese medicine, and introduce some clinical cases along with a review of the literature.

Keywords

Cancer metabolism; Aerobic glycolysis; Warburg effect; Inflammation; Immunity; Diet

Introduction

In recent years, there has been considerable progress in cancer treatment, with the development of many anti-cancer drugs, which are mainly molecular-targeting treatments. These new treatments have improved the survival rates of cancer patients; however, there are a number of problems with these new types of cancer treatments.

In Japan, the 5-year relative survival rate of cancer patients who were diagnosed between 2006 and 2008 was 62.1%, which was improved from the rate between 1993 and 1996, which was 53.2%.[1] For advanced cancers with metastasis, the 5-year survival rate of patients also improved, from 10.3% in patients diagnosed between 1993 and 1996, to 13.6% in those diagnosed between 2006 and 2008,[1] although this is still far from ideal. Surgery, chemotherapy, and radiotherapy are currently very common standard treatments for cancer. However, there are 3 major problems. First, in advanced cancer, there is little hope that such standard treatments will cure the disease. Second, adverse side effects accompanying standard cancer

treatments put many patients under large amounts of distress, although many drugs have also been developed for such side effects. Third, an increase in medical expenditure is a serious problem. The national medical expenditure of Japan in 2015 was 372 billion US dollars (42 trillion and 364 billion yen at a rate of 0.0088 dollar per yen).[2] In the recent 10 years, healthcare costs increased by about 88 billion US dollars (10 trillion yen at a rate of 0.0088 dollar per yen). An increase in the availability of new and expensive anti-cancer drugs may be one cause of this increase in healthcare cost.

As mentioned above, there are a number of problems with current cancer treatments, and we believe that little consideration regarding the root cause of the cancer may be the reason for these problems. Otto Warburg suggested that a change in the energy metabolism of cells due to a lack of oxygen is the root cause of cancer.[3] Namely, cells exposed to a low oxygen environment will alter their metabolism to generate energy mainly via glycolysis, and as a result, lactic acid will be overproduced. Excess lactic acid

will create an acidic tumor microenvironment and promote inflammation, which will enable cancer cells to develop and progress more easily. Therefore, cancer cells have unique metabolic characteristics that distinguish them from normal cells. This leads to the question of whether it is sufficient to treat cancer just as a malignant tumor that unexpectedly emerged in the body, without considering its root cause.

In reconsidering approaches of cancer treatment, the principles of Chinese medicine, "*Fuzheng Quxie*" and "*Zhibing Qiuben*" are very useful.[4] These principles demonstrate the importance of viewing cancer treatment in a way as to not treat the resulting cancer, but to investigate the root cause of the cancer and to correct it. Specifically, suppressing the unique metabolic reactions of cancer cells that are part of the cause of the cancers, improving chronic inflammation associated with the promotion and development of cancers, and taking the functions of immune cells into consideration are necessary for cancer treatment. In other words, treating cancer as a metabolic disease is viewed to be important.

Cancer as a Metabolic Disease

Hanahan and Weinberg stated 8 essential physiological characteristics of cancer cells as the hallmarks of cancer,[5] as follows: 1) sustaining proliferative signaling; 2) evading growth suppressors; 3) resisting cell death; 4) enabling replicative immortality; 5) inducing angiogenesis; 6) activating invasion and metastasis; 7) reprogramming of energy metabolism, and 8) evading immune destruction. They suggested that these characteristics are acquired by genomic instability, leading to increased mutability. On the other hand, Warburg suggested that when normal cells cannot generate adenosine triphosphate (ATP) via oxidative phosphorylation (OxPhos) due to the shortage of oxygen, normal cells will begin to generate ATP mainly via glycolysis for their survival. Namely, he proposed that this change in energy metabolism was the root cause of cancer.[3]

Epidemiological data showed that people who develop cancer owing to their genetic backgrounds were less than 5% of the total, and that most

cancers are caused by particular lifestyles (diet and obesity: 30%; smoking: 30%; sedentary habits: 5%; occupational factors: 5%; reproductive factors: 5%, etc.).[6] It is controversial whether the root cause of cancer is the accumulation of genome mutations or a change in energy metabolism. However, many reports show that a change in energy metabolism promotes genome mutations that are associated with the further progression of cancer, and therefore the view of cancer as a metabolic disease appears to be very important.[7] We describe the unique metabolic reactions of cancer below.

i) Warburg effect (aerobic glycolysis)

This is a unique metabolic state of cancers, in which cancers create ATP via activated glycolysis using very little oxygen, even in the presence of sufficient oxygen, to make ATP via OxPhos. The uptake of glucose increases the production of lactic acid, and the resultant protons are transported out of cancer cells through the Na^+/H^+ exchanger. The lactic acid causes the environment around the cancer cells to become acidic, which is one of the characteristics of the tumor

microenvironment.[8] Advantages of the activated glycolysis of cancer cells are suggested to be effective ATP production without depending on molecules from the blood flow, and the generation of macromolecules and NADPH via the pentose phosphate pathway and other pathways for biosynthesis and redox reactions.[9]

ii) Na^+/H^+ exchanger

As mentioned above, activated glycolysis increases the production of lactic acid inside the cancer cells, and the Na^+/H^+ exchanger is activated to remove the protons generated by lactic acid from the cancer cells. Therefore, the intracellular pH of cancer cells is alkaline (7.2–7.4). In contrast, the extracellular pH surrounding cancer cells is acidic (6.5–7.0). Such an abnormal state of pH regulation may be associated with the initiation of cancer, and an acidic tumor microenvironment is associated with the development and progression of cancer, angiogenesis, metastasis, and drug resistance. Interfering

with the pH regulation of cancer cells has been considered as a possible therapeutic strategy.[10, 11]

iii) Insulin-like growth factor (IGF) signaling pathway

The IGF signaling pathway is reported to be an important proliferative pathway of cancer cells. The excess IGF in the body activates mammalian target of rapamycin (mTOR) through the phosphoinositide-3-kinase-Akt pathway, and hence there is a risk of the promotion of cancer cell progression. The incidence rate of cancer is known to be higher in people with diabetes than in people without diabetes, and the mortality rate is also known to be higher in diabetic cancer patients than in cancer patients without diabetes. Furthermore, it was reported that insulin as well as IGF also activates mTOR.[12] The anti-diabetic drug metformin was shown to decrease the morbidity and mortality of cancer patients by the suppression of mTOR followed by the activation of AMP-activated protein kinase, and many clinical

studies on metformin have been performed.[13, 14]

iv) Fatty acid synthase (FASN)

Fatty acids (FAs) are essential components of the cellular membrane. There are exogenous FAs from the diet as well as endogenous FAs that are synthesized in the human body. In normal cells, FASN converts excessive carbohydrates into FAs, and they are stored as triacylglycerols. However, because exogenous FAs are usually sufficient for the human body, the importance of FASN in normal cells is considered to be minimal. On the other hand, it is reported that FASN is activated in cancer cells, including precancerous lesions, and the activation of FASN as well as the activation of glycolysis are thought to be metabolic changes required for adaptation to the tumor microenvironment (low oxygen, low nutrition, acidic state, etc.). The suppression of FASN is considered as a possible therapeutic strategy for cancer, and the polyphenol epigallocatechin-3-gallate, which is

contained in green tea, and ursolic acid, which is contained in Japanese plums, have been shown to suppress FASN.[15, 16]

v) Inflammation: Nuclear factor-κB (NF-κB)

As Rudolph Virchow previously mentioned, there are many similarities between inflammatory reactions, such as the process of wound healing, and the process of cancer development.[17, 18] Many cancers develop as a result of chronic inflammation, and a tumor microenvironment that largely comprises inflammatory cells is known not only to promote the proliferation of cancers, but also their survival and migration. Furthermore, it was suggested that an inflammatory tumor environment is associated with immune reactions and resistance to treatment.[19, 20] Excessive inflammation is thought to be a target for cancer treatment, and NF-κB, a transcription factor with an important role in regulating inflammatory reactions, was shown to be constantly overactivated in many cancers.[21] In lung cancers positive

for the epidermal growth factor receptor (EGFR) mutation, an increased effect of the EGFR-tyrosine kinase inhibitor (TKI) was shown by the suppression of NF-κB, and hence the effect of EGFR-TKI was reported to depend on the state of NF-κB.[22]

vi) Epithelial mesenchymal transition (EMT)

EMT is known as a biological process of cancer cells associated with invasion and metastasis. It was reported that EMT is the transition from epithelial cellular characteristics to mesenchymal characteristics, which enables cancer cells to invade, metastasize, and acquire resistance to cancer treatment.[23, 24] An analysis of circulating tumor cells (CTCs) from breast cancer patients showed that the proportion of epithelial CTCs to mesenchymal cells changes depending on the reactions against cancer treatment or the degree of progression of cancer.[25] Furthermore, inflammation is known to promote EMT.[19, 20]

Prospects of Cancer Treatment – Fusion of Eastern and Western Medicine

Incorporating the ideas of Chinese medicine is remarkably important towards improving cancer treatment. Chinese medicine views cancer as a disease that is expressed locally, but is actually due to an underlying constitutional disorder of the body. Therefore, there should be more focus on treatment of the entire body than on the locally existing cancer, specifically in advanced stages of cancer. The basic strategy for cancer treatment in Chinese medicine is "*Fuzheng Quxie*", which is to remove factors promoting the cancer and to enhance the immune system of the body. Furthermore, the concept of "*Zhibing Qiuben*", which is to clarify the root cause of the disease and to treat this root cause, is very important.[4] In Chinese medicine, pathologies such as stagnation of spirit (*qi zhi*), blood stasis (*yu xue*), phlegm-dampness (*tan shi*), and heat toxin (*re du*) are thought to be important factors associated with the initiation and progression of cancers. As these factors are also associated with metabolic diseases, the view of Chinese medicine supports our idea that treatments for cancer from the view

of cancer as a metabolic disease are required.

As mentioned above, there is a difference in the metabolism of normal cells and cancer cells. Factors involved in abnormal cancer cell metabolism are what cause the promotion of cancer, and without improving these factors, current standard cancer therapies will not be sufficiently effective. Namely, it is necessary to gain information regarding the patients' daily diet and lifestyle, to improve or remove factors that may cause cancer. In particular, the Warburg effect (aerobic glycolysis), Na^+/H^+ exchanger, IGF signaling pathway, and the activation of FASN should be considered, and whether there is an excess intake of sugar, salt, and IGF hormone should be evaluated and improved as required. For the suppression of chronic inflammation, not only should lifestyle-associated diseases, such as obesity and diabetes, be treated appropriately and improved, but the intake of more plant-based foods that contain a large amount of antioxidants, such as fresh vegetables and fruits, as well as natural compounds, are expected to be useful. In all cases, Chinese medicine provides abundant treatment options,

such as activating blood and resolving stasis (*Huoxue Huayu*), dispelling phlegm and resolving dampness (*Qutan Huashi*), and clearing heat and removing toxin (*Qingre Jiedu*), etc. To suppress cancer metabolism and inflammation is to suppress the progression, metastasis, and EMT of cancer, and is expected to improve the function of the immune system, which will subsequently decrease a cancer's resistance to treatment.

As stated above, the idea of focusing on the unique metabolism of cancer cells and treating cancer as a metabolic disease resembles the view of Chinese medicine for cancer treatment, which is expected to become increasingly important in the future. We will now introduce 3 clinical cases of cancer treatment as a metabolic disease. All the clinical case studies were performed in accordance with the ethical principles stated in the 1995 *Declaration of Helsinki* and were approved by the institutional review board of the Japan-Multinational Trial Organization.

Clinical Cases

1) Male patient (fifties) with recurrent lung adenocarcinoma

A man in his late fifties who was diagnosed with recurrent lung adenocarcinoma after right upper lobectomy visited our clinic. He had received tegafur-uracil therapy after surgery; however, his lung cancer recurred with multiple bone metastases (Fig. 1A).

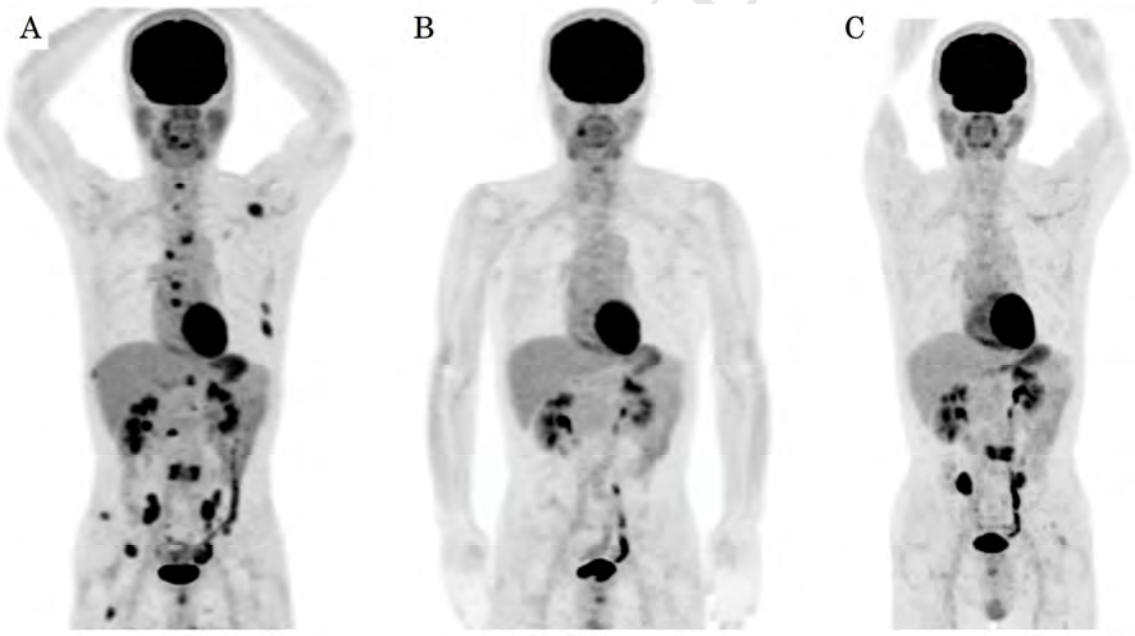

Figure 1 PET-CT image of a recurrent lung cancer patient

A: At the time of recurrence, multiple bone metastases were displayed. B: Twelve months after the start of EGFR-TKI treatment, PET-CT imaging displayed complete remission. C: Twenty-seven months after treatment,

recurrent bone metastases of the lumbar spine were observed.

We provided the patient, who had an EGFR mutation, with instructions on dietary and life habit improvements, and he started afatinib (40 mg/day). Three months after the start of the treatment, the dose of afatinib was reduced (to 30 mg/day), because of dermatitis and diarrhea. Then, the dose was again reduced (to 20 mg/day), owing to the continuation of diarrhea. Positron emission tomography-computed tomography (PET-CT) scans displayed complete remission for over one year (Fig. 1B). However, 27 months after the start of EGFR-TKI treatment, his bone metastases recurred again (Fig. 1C). His progression-free survival (PFS) was 27.3 months.

In this case, EGFR-TKI with the suppression of cancer metabolism and inflammation by dietary and life habit improvements showed a longer PFS than previous studies and hence may be considerably effective.[26] This case was included in our previous retrospective study to

investigate the effects of an alkaline diet on EGFR-TKI therapy in non-small cell lung cancer patients with EGFR mutations.[27]

2) Male patient (seventies) with multiple gastric cancer (signet-ring cell carcinoma)

A man in his early seventies was found to be positive for fecal occult blood in a routine medical examination, and then went to a local clinic for further examinations. Upper gastrointestinal endoscopy displayed multiple polypoid lesions in the stomach (Fig. 2A), and a subsequent histological examination confirmed signet-ring cell carcinoma. Although subtotal pylorogastrectomy was recommended, he refused the surgery because of its high invasiveness, and he visited our clinic for consultation regarding alternative treatments.

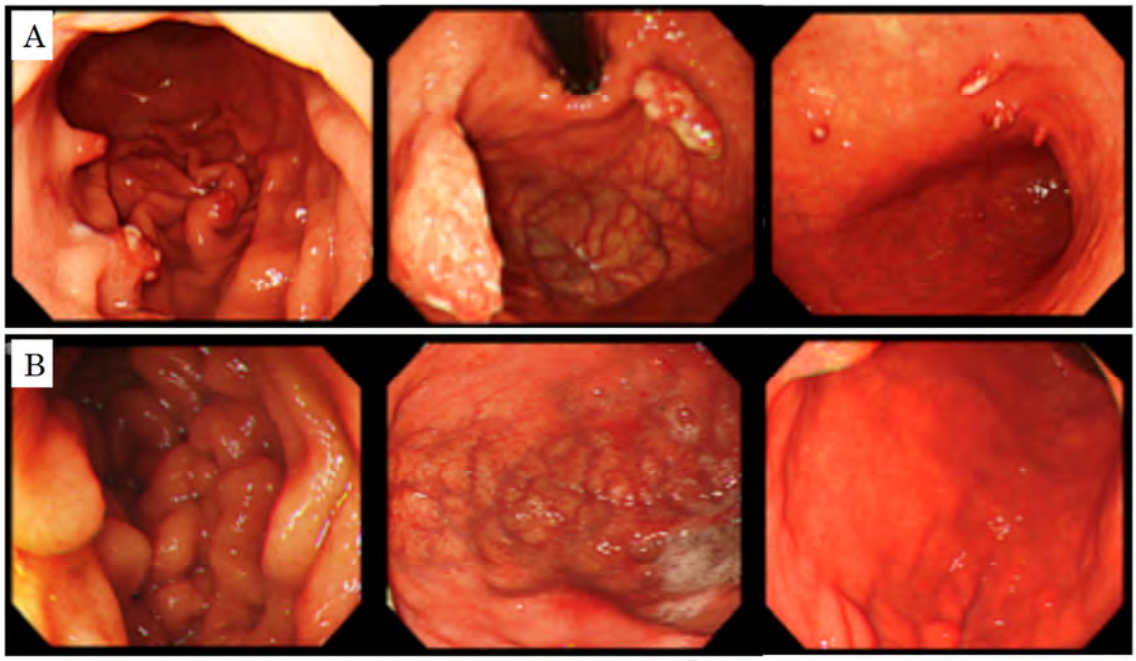

Figure 2 Upper endoscopic findings of a patient with multiple gastric cancer

A: At the time of diagnosis, multiple polypoid lesions were observed in the stomach. B: Three years after the start of treatment, the tumorous lesions had almost completely disappeared.

We provided the patient with sufficient instructions for dietary and life-habit improvements. After undergoing endoscopic polypectomy, he was administered with a low dose of S-1 (20 mg/week) and lentinan (2 mg/week) via intravenous infusion, with the purpose of immunostimulation. In addition, plum extract (10–15 g/day) was given as

appropriate. Japanese plum extract is a health supplementary food (UME EKISU from Nakano BC, Wakayama, Japan), made by boiling down large amounts of green Japanese plums. It contains triterpenes (ursolic acid and oleanolic acid), which have been shown to suppress inflammation and to have anticancer effects both *in vivo* and *in vitro*.[28, 29]

Three years after treatment, with no sign of clinical symptoms and side effects, upper gastrointestinal endoscopy showed that the multiple gastric cancers had almost vanished (Fig. 2B). This case suggests that the suppression of cancer metabolism and inflammation may result in outstanding effects of low dose anti-cancer agents and immunostimulatory drugs.

3) Female patient (seventies) with malignant gastric lymphoma (diffuse large B-cell lymphoma)

A woman in her mid-seventies had mild gastric pain that was controlled by herbal medicine. She had an upper gastrointestinal endoscopy because

of strong stomach pain (Fig. 3A). She was suspected of having gastric cancer, and a detailed examination showed malignant lymphoma (diffuse large B-cell lymphoma). Although she was recommended to take anti-cancer agents, she was of advanced age and was anxious about the side effects, and hence refused treatment. She then visited our clinic for consultation regarding alternative therapies.

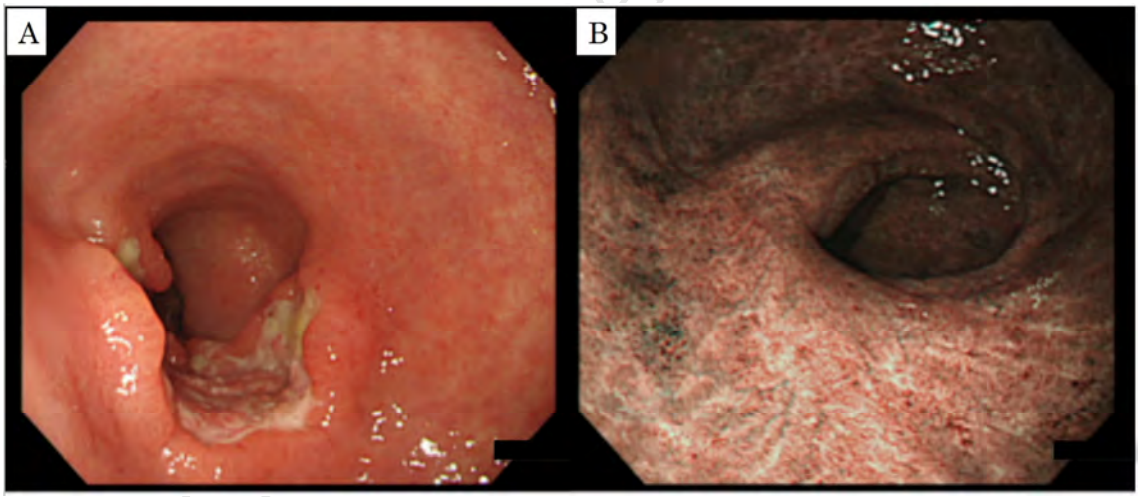

Figure 3 Upper endoscopic findings of a diffuse large B-cell lymphoma patient

A: At the time of diagnosis, ulcerative tumorous lesions were observed in the stomach. B: Eight months after the start of the treatment, the

ulcerative tumorous lesions were improved.

As the patient was very fond of sweets, such as cake, she was given a sufficient amount of instructions on dietary and life-habit improvements. In addition, she was given plum extract (10–15 g/day), which was the same as in case 2. After the start of treatment, her gastric symptoms gradually improved, and upper gastrointestinal endoscopy 8 months after her diagnosis displayed no signs of a tumorous lesion (Fig. 3B). This case was an example in which cancer was improved without the use of an anti-cancer agent, and thus suggests that the suppression of cancer metabolism and inflammation on their own may be remarkably effective.

Conclusions

Here we have provided an overview of the treatment of cancer as a metabolic disease, introducing some examples of actual clinical cases. The idea of

suppressing cancer metabolism and inflammation, which promote cancer, and enhancing immune functions coincide with the principles of Chinese medicine, such as *Fuzheng Quxie* and *Zhibing Qiuben*. These approaches to cancer treatment may result in high treatment efficacy with minimum side effects, and have the possibility of reducing medical expenses. Further investigations should therefore be performed in the future.

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