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Systemic Buffers in Cancer Therapy: The Example of Sodium Bicarbonate; Stupid Idea or Wise Remedy?

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Abstract

Despite recent therapeutic progress, cancer remains a major cause of death in industrialized countries. As a consequence, alternative treatments attract the attention of a growing number of patients. Among these therapies, the use of sodium bicarbonate to fight cancer has gained considerable interest. According to self-medication reports available on the internet, sodium bicarbonate is viewed by many patients as a simple, costless and efficient anti-cancer agent. Although no clinical study has demonstrated an anti-cancer activity of sodium bicarbonate up to date, emerging experimental reports indicate, that sodium bicarbonate may slow the progression of cancer. Here, we highlight the rationale to use sodium bicarbonate in cancer therapy and further enumerate experimental evidence for its anti-tumoral activity. Finally, we speculate about a future role of sodium bicarbonate in cancer therapy.

Keywords: Sodium bicarbonate; Cancer; Therapy; pH; Acidity; Baking soda

Introduction

The incidence of cancer is rising worldwide and so is the need for adequate therapies. Improvements in surgery and chemo-radiotherapies as well as novel treatment modalities including targeted therapies and immunotherapies have significantly prolonged survival of cancer patients. Nevertheless, cancer remains a lethal disease, in particular in advanced stages. Based on this perspective, cancer patients frequently turn to alternative medicine, either in the hope of cure or in order to relieve symptoms. Internet provides information on magical remedies, presumably curing cancer, hence encouraging cancer patients to self-medication. In this context, emerging interest is drawn to sodium bicarbonate. Multiple patients' reports, blogs and physicians' testimonials praise the anti-tumor activity of sodium bicarbonate on the internet. Different theories were raised to explain its anti-cancer properties. One example is the ability of sodium bicarbonate to buffer tumor acidity and hence block acidity induced tumor growth. Despite these frequent reports, clinical data on the role of sodium bicarbonate treatment in cancer is still missing. Nonetheless, emerging experimental data support a beneficial effect of sodium bicarbonate on tumor growth, underlining a possible role of sodium bicarbonate in cancer therapy. In this article, we review the rationale of using sodium bicarbonate in cancer by focusing on the effect of tumor acidity on cancer progression. We further highlight the experimental evidence for an anti-cancer efficacy of sodium bicarbonate. Finally, we underline the hurdles in using sodium bicarbonate in cancer patients.

The Effect of Tumor Acidity on Cancer Progression

The tumor microenvironment is a complex structure composed of different cell types besides cancer cells themselves [1]. In contrast to normal tissue, the physico-chemical microenvironment of solid tumors has its own features including areas of hypoxia and acidic pH [2,3]. The latter is a consequence of an increased production of acidity by tumor cells in combination with a poor vascular circulation and blood supply [4]. In turn, acidity profoundly influences the biology of tumors (Figure 1). In fact, acidity controls cancer cells in several aspects. Firstly, acidity can be mutagenic, presumably by inducing DNA double-strand breaks by reactive oxide species or by blocking the topoisomerase II [5-7]. Hence, acidic pH actively contributes to the genetic instability of cancer cells. Secondly, evidence suggest that acidity promotes metastasis formation. Indeed, melanoma cells pre-exposed to acidic medium metastasized more frequently to the lungs when injected into the tail vein of mice [8-10]. This was associated with up-reguation of the proteolytic enzymes MMP-2, MMP-9, cathepsin B, and cathepsin L, suggesting that acidity favors basement membrane and extracellular matrix degradation by cancer cells [8,11]. Consistent with the observation that cancer cells display a more aggressive phenotype following exposure to acidity, it was reported that low pH values increase the motility and invasiveness of cancer cells [10,12]. In line with these observations, regions of highest tumor invasion were shown to feature lowest pH in a dorsal chamber window model [13]. Furthermore, acidic pH promotes the disruption of cell-cell junctions, an important step that allows tumor cells to move into the surrounding tissue [14]. Indirect evidence for a role of acidity in promoting tumor metastasis has also been reported. For example, a high expression of carbonic anhydrase IX, an enzyme that acidifies tumor extracellular pH, is associated with metastasis [15]. Besides, extracellular pH was predictive of metastasis in dogs presenting spontaneous sarcomas [16].

In addition to its effects on cancer cells, acidity influences the efficacy of conventional cancer therapies. For instance, the acidic extracellular pH reduces the uptake of weak base chemotherapeutics such as doxorubicin by decreasing its cellular uptake [17,18]. Similar observations were made for mitoxantrone and topotecan [19]. Furthermore, acidity was reported to contribute to resistance of cancer cells by increasing drug efflux through an augmented expression of p-glycoprotein [20]. Besides its influence on chemotherapies, acidity was shown to render cancer cell resistant to radiotherapy. Indeed, radiation induced cell death is reduced in cancer cells cultured in acidic medium compared to physiological medium [21-23]. The mechanism involves a prolonged G2 arrest after irradiation in acidity, resulting in increased DNA damage repair.

As mentioned above, the tumor microenvironment consists of several other cell types apart from cancer cells. Among these, immune cells play a major role in tumor rejection. Over time, cancer evades

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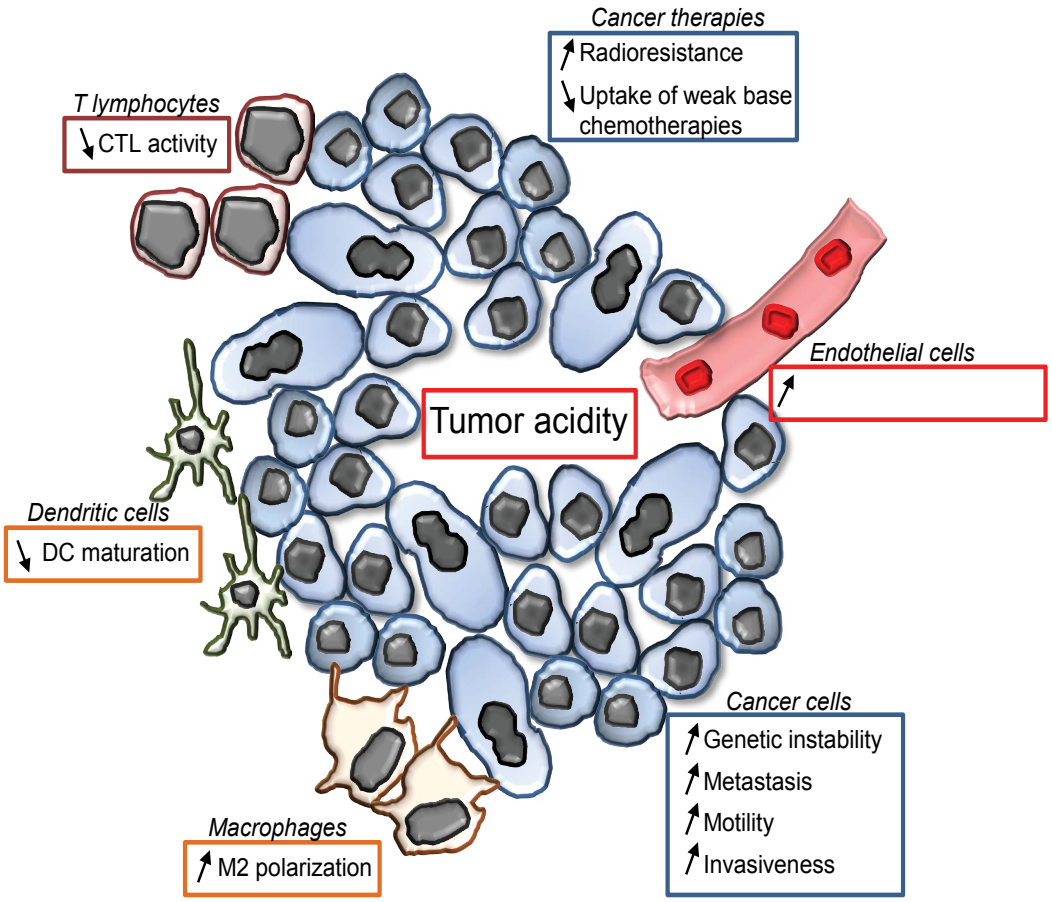

Figure 1: Complex model of 3,4-DCQ-1-COOR with respiratory syncytial virus (RSV) fusion protein (PDB: 3IXT). R (within the red rectangle) represents any hydrophobic group. R is buried in a hydrophobic pocket formed by B/TYR87, B/ALA43, B/PRO40, and A/TYR91. B means basic. A means acidic.

antitumor immune response, enabling tumor progression [24]. Recent studies have shown that tumor acidity represents a hostile environment for tumor infiltrating T lymphocytes [25,26]. *In vitro*, exposing tumor-specific $CD8^+$ T lymphocytes to acidic pH promotes reversible anergy characterized by impaired cytolytic activity and cytokine secretion. *In vivo*, enhancing tumor pH with proton pump inhibitors increased the efficacy of immunotherapy, identifying acidity as a mechanism of immune escape [26]. Consistent with these observations, the increased production of lactic acid by tumor cells also markedly impedes the function of human T cells [27,28]. Furthermore, lactic acid modulates dendritic cell maturation and antigen presentation, which further contributes to immune escape of tumors [29]. The effect of lactic acid is not limited to the adaptive immune system but also influences innate immunity. Macrophages are among the most abundant cells present in the tumor microenvironment. Depending on the condition, they undergo a classical (M1) or alternative (M2) activation [30]. Whereas M1-polarized macrophages exhibit antitumor activity, M2-polarized macrophages promote cancer growth. Recent findings have demonstrated that lactic acid induces an M2-like polarization of tumor-associated macrophages [31]. This effect seems to be mediated by acidity since macrophages cultured in low pH conditions acquire an M2 phenotype [32].

Finally, the effect of tumor acidity on endothelial cells has been reported but needs further characterization. Nevertheless, it was suggested that acidity would not impair the angiogenic response necessary for tumor growth. In the rat aortic ring model, acidity reduced the angiogenic response but did not block it [33]. In addition, lactic acid might also contribute to angiogenesis by inducing the production of pro-angiogenic factors such as interleukin-8 and bFGF in endothelial cells following its uptake through the lactate transporter MCT1 [34,35].

Sodium Bicarbonate: The Experimental Evidence

As mentioned above, tumor acidity favors tumor progression. Hence, therapeutic interventions that target acidity were explored in cancer [36,37]. Amidst these strategies, systemic buffers such as sodium bicarbonate were used successfully to increase intratumoral pH (Table 1). Initially, sodium bicarbonate was shown to increase tumoral pH in mice bearing breast tumor xenografts, resulting in an improved anti-cancer efficacy of doxorubicin [38]. The feasibility of using sodium bicarbonate was further demonstrated in mathematical models [39]. Computer simulations demonstrated that ingestion of sodium bicarbonate effectively decreases tumor acidity without modifying blood and tissue pH. Furthermore, the resulting change in tumoral pH decreases tumor growth and invasion. Additional studies in tumor mouse models confirmed these observations [40]. Breast tumor xenografts were generated in immunodeficient mice. Mice were then randomized into control and treatment groups receiving or not sodium bicarbonate in the drinking water. Mice provided with sodium bicarbonate lived significantly longer and displayed a reduction in number and size of metastases of the lung, bowel and diaphragm. Of note, sodium bicarbonate had no effect on primary tumor growth and did not induce significant toxicity. Magnetic resonance spectroscopy confirmed that sodium bicarbonate increases the intratumoral pH.

Effects	Model	References
Increases tumor pH	• MCF-7 human breast cancer xenografts in mice • CH3 murine mammary carcinoma • Computer simulation • MDA-MB-231 human breast cancer xenografts in mice • MDA-MB-231 cancer cells grown in mice dorsal skin-fold window chambers • HCT116 human colon cancer cells grown in mice dorsal skin-fold window chambers	[13,38,39,40,43]
Increases the efficacy of weak base chemotherapy	• MCF-7 human breast cancer xenografts in mice • CH3 murine mammary carcinoma	[38,43]
Decreases metastasis	• MDA-MB-231 xenografts • Intrasplenic injection of MDA-MB-231 cancer cells • Tail vein injection of PC3M prostate cancer cells	[40]
Reduces tumor growth	• Transgenic mouse model of prostate cancer • HCT116 human colon cancer cells grown in mice dorsal skin-fold window chambers	[13,41]

Table 1: Experimental evidences of the effects of sodium bicarbonate in cancer.

No disturbance of blood electrolytes was noted after treatment. In particular, it did not lead to metabolic alkalosis [40]. In the same study, sodium bicarbonate reduced liver metastasis of human breast cancer cells injected into the spleen. In addition, it also decreased metastasis formation following tail vein injection of PC3M human prostate cancer cells. In contrast, in the same model, sodium bicarbonate failed to significantly decrease metastasis when B16 mouse melanoma cells were injected. Although the precise mechanism underlying this discrepancy not being identified, authors speculated that, as B16 cells proliferated faster, their rates of acid production might simply overpass the buffering capacities of sodium bicarbonate [40].

The effect of sodium bicarbonate was also tested in a transgenic mice model of prostate cancer [41]. In this model, the oncoprotein SV40 T antigen is under the control of the probasin promoter, resulting in prostate intraepithelial neoplasia before the age of 5 weeks and progressing to invasive cancer around the age of 5 to 8 weeks [42]. When sodium bicarbonate was initiated after the age of 6 weeks, this did not block prostate cancer progression; primary tumor growth characteristics of concerned mice were similar to the ones of untreated mice. In contrast, if started at the age of 4 weeks, sodium bicarbonate significantly reduced development of prostate cancer. At necropsy, prostate hyperplasia was present in most of these mice and 30% displayed small cancer foci. Notably, the pH of early treated mice was significantly higher than in untreated or late treated mice. This suggests that, by targeting acidity in intraepithelial neoplasias, sodium bicarbonate may prevent the development of invasive prostate cancer.

Finally, sodium bicarbonate was also tested for its effect on tumor growth within a mouse dorsal skin window chamber [13]. It was reported that the growth of the human colon cancer cells HCT116 was significantly reduced by sodium bicarbonate. Furthermore, the ability of sodium bicarbonate to increase the tumor pH was demonstrated. More importantly, it was shown that, whereas pH values at the center of the tumor did not significantly vary between control and bicarbonate treated mice, they were markedly increased at the invasive front. This further suggests a role of sodium bicarbonate in reducing tumor invasion by targeting acidity.

Finally, sodium bicarbonate was shown to increase the anti-cancer efficacy of weak base chemotherapies, as their cellular uptake was improved by increased extracellular tumor pH. MCF-7 human breast cancer cells were injected into the mammary fat pads of immunodeficient mice, and tumor growth was monitored. Whereas tumor growth of mice treated with sodiumbicarbonate alone was similar to control mice, in combination, sodium bicarbonate significantly increased the anti-cancer efficacy of doxorubicin [38]. Similar results were reported for mitoxantrone in a mammary carcinoma mouse model [43].

Sodium Bicarbonate: Is it a Safe Remedy?

Major concerns exist regarding the systemic use of sodium bicarbonate in patients, principally the development of metabolic alkalosis and its complications as well as hypernatremia. In addition, abrupt cessation of sodium bicarbonate might also result in adverse effect. Interestingly, several articles exist in the literature reporting the toxicity of chronic ingestion of sodium bicarbonate [44-47]. Indeed, baking soda, a common household product containing sodium bicarbonate has frequently been taken as an antacid to relieve heartburn. As expected, excessive ingestion of baking soda results in serious electrolyte imbalance requiring medical attention. Gastrointestinal symptoms such as abdominal pain, diarrhea, vomiting are frequently reported in this patients coupled with other symptoms including lethargy and weakness [45]. Respiratory compensation was also noticed with blood hypercapnia. Adverse effects were already reported in patients taking less than two teaspoons of baking soda with one teaspoon containing 4.8 g of sodium bicarbonate [45].

Contrariwise, chronic administration of sodium bicarbonate without major side effects was reported in patients with sickle cell disease or chronic metabolic acidosis [48-50], suggesting that ingestion of sodium bicarbonate is feasible under medical supervision. Furthermore, sodium bicarbonate is part of cancer treatment in alternative medicine and seems to be well tolerated at a daily dose of 12 g per day [51]. Of note, a case report of a 79-year-old man with advanced renal cell carcinoma who discontinued conventional treatment and initiated a self-medication consisting of vitamins, supplements and 60 g of sodium bicarbonate daily for ten months revealed a good tolerance of this high dose of sodium bicarbonate without development of side effects [39].

Whereas chronic ingestion of sodium bicarbonate can induce toxicity, its administration over a short time period might be better tolerated. In this context, sodium bicarbonate could be used as an adjunct to weak base chemotherapies in order to increase their efficacy. Furthermore, it might be worth testing a combination of sodium bicarbonate with radiotherapy or immunotherapies, possibly improving their efficacy. Novel therapies are preferentially tested in patients with advanced stages of cancer that progressed under conventional treatment. Hence the probability to demonstrate the anti-cancer efficacy of a new treatment might be lower, necessitating a large cohort to show an effect. The costs of such studies are generally high and funding may be a challenge. Since no financial profit is expected by the prescription of sodium bicarbonate, it might be even more difficult to find sponsors ready to invest in such studies.

Conclusions

Many internet testimonials report of self-medication of sodium bicarbonate by cancer patients. However, despite a scientific rationale

to use bicarbonate as a cancer treatment and emerging pre-clinical studies pointing to its anti-cancer efficacy, physicians remain skeptical towards this approach. Concerns are raised with respect to its efficacy and safety. Future experimental studies are necessary to better characterize the mechanism underlying the effect of sodium bicarbonate in cancer. Furthermore, clinical trials are needed in order to demonstrate its activity either as single treatment or adjunct therapy in patients. In addition, the tolerance and safety of sodium bicarbonate needs to be investigated in patients. Of note, since the sale of sodium bicarbonate does not generate any financial benefit, readiness to test it in costly clinical trials might be very limited.

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