

Therapeutic Potential of Glutathione Augmentation in Cancer Patients Receiving Chemotherapy or Radiotherapy

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Abstract: The majority of cancer patients receiving conventional medical therapy receive chemotherapy, radiotherapy, surgery or palliative support. Nutritional support is increasingly recognized as vital to successful treatment. Glutathione (GSH) is a naturally-occurring tripeptide in human cells that serves many important functions, including antioxidant regulation, detoxification, protein synthesis and repair, immune modulation, and redox signaling. Altering glutathione levels has been demonstrated to have significant effects in chemotherapy/radiotherapy outcomes as well as influence on retarding cachexia. This review article summarizes some of the most notable findings, suggesting that up-regulation of glutathione through nutritional intervention has a potential to be integrated into a holistic approach to cancer treatment.

Key Words: Glutathione; Cancer; Chemotherapy; Radiotherapy; Cachexia; Nutrition; Immunocal

Introduction

The search for selective injury or destruction to cancer cells while limiting concomitant damage to normal cells has been the cornerstone of cancer therapy. Surgical excision is feasible if the tumor has not metastasized or a debulking procedure is warranted.

Chemotherapy represents a controlled poisoning of the patient based on the idea that rapidly proliferating cancer cells are more sensitive to the toxin than normal cells. Unfortunately, many effective chemotherapeutic agents may produce adverse side effects.

Radiotherapy works in a similar way. The cancerous area is targeted for radioactive bombardment and the tumor is theoretically more sensitive to the radiation than the surrounding healthy tissues. This too carries potentially significant adverse effects for the patient.

Pretreatment or concomitant treatment with agents that both enhance the selective toxicity of chemo/radiotherapy to tumor cells while protecting healthy cells from damage represents a welcome addition to standard approaches to cancer therapy. The naturally-occurring tripeptide glutathione (GSH) has been increasingly studied to play these roles.

GSH plays several critical roles in the normal physiology of cells, including antioxidant regulation, detoxification, protein synthesis and repair, immune modulation and redox signaling [1]. Both increasing GSH levels and decreasing GSH levels have been investigated in the search for effective glutathione modulatory approaches in oncology. This present review article offers a synopsis of some historical findings.

Glutathione Modulation in Cancerous and Healthy Cells

Most studies reveal a paradoxical situation, where cancer cells are high in glutathione [2], but normal cells in cancer patients are low in glutathione compared to a healthy population [3]. Notably, not only do low GSH levels correlate with the susceptibility of individuals to develop cancer [4, 5], but advanced cancer patients also reveal even lower total body GSH levels [6]. More importantly, elevated GSH in normal cells may offer increased protection from the side effects of chemotherapy and radiotherapy and offer an advantage in immune function and muscle preservation [7].

Experimental evidence shows that the level of GSH synthesis affects the susceptibility of both normal and cancerous cells to damage from chemical toxins or radiation [8]. High GSH levels help protect cells from the harmful effects of chemotherapy [9, 10]. Results would be ideal if GSH levels were high in normal cells and low in tumorous cells [11], but as stated, most human cancer cells appear to have higher GSH levels than normal cells. Cancer is a rare example where these otherwise tightly regulated GSH levels are exceeded [12]. This is a consequence of lack of normal GSH regulatory mechanisms in cancerous cells [8]. Because the tumor cells high in GSH often show resistance to chemotherapy, some researchers have tried to reduce GSH levels in cancerous cells with GSH-depleting drugs like BSO (buthionine sulfoximine) [13]. A limiting consequence of the use of BSO is its non-specific action, simultaneously reducing GSH levels in healthy cells as well, resulting in the magnification of side effects, thereby limiting the practicality of this approach [14].

Oddly enough, the precursors that usually raise GSH levels in normal cells often cause the opposite effect in cancerous cells, causing GSH levels to fall [15]. This is due to a strong negative feedback loop in cancerous cells with aberrant GSH production (Figure 1) [16]. These cells will

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down-regulate GSH production when intermediate steps (e.g., glutamyl-cysteine) of GSH production are reached. This negative feedback inhibition leaves cancerous tissue more susceptible to damage or destruction while normal cells, with normal GSH metabolism, are left with better defense mechanisms [16].

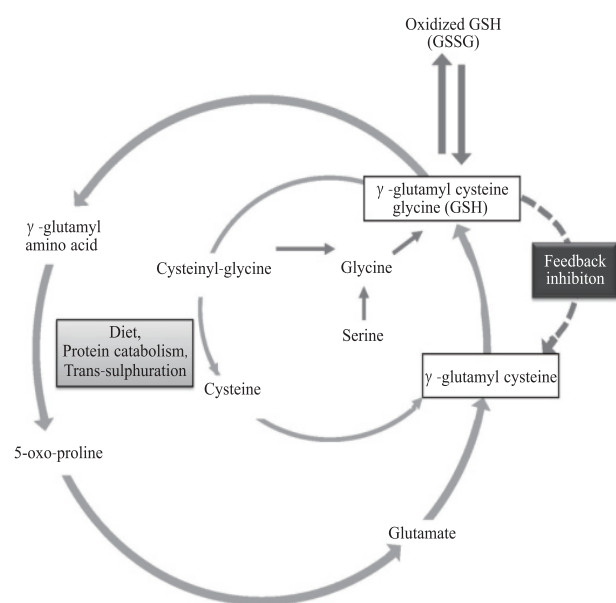


Figure 1. Biochemical pathway of glutathione production and regulation. Glutathione (gamma-glutamyl cysteine glycine) inhibits its own production by down-regulating gamma-glutamyl cysteine.

Clinical Trials

As far back as 1986, an NIH study demonstrated that adding the GSH-promoting drug OTZ (2oxothia2olidine-4-carboxylic acid) to human lung cancer cells, there was no increase in GSH levels in the cancer cells, whereas surrounding normal cells increased their levels [17]. Going one step further, McGill University researchers Sylvain Baruchel, Gerry Batist, and their team have demonstrated that OTZ could even paradoxically deplete GSH content in breast cancer cells while normal cells profited [11]. Another study from McGill University led by Dr. Gustavo Bounous has generated similar selective GSH modulatory results, using whey protein isolates containing specific GSH precursors [16].

Subsequently, studies have been performed on patients with metastatic carcinoma, who were given this specially prepared whey protein isolate for six months. Although it did not cure the cancer, a significant proportion showed either tumor regression/stabilization or normalization of hemoglobin and white blood cell counts [18]. The same researchers have demonstrated that elevated GSH levels may enhance certain chemotherapeutic agents.

Another Canadian team has studied patients with ad-

vanced progressive cancer, using toxic doses of acetaminophen as the chemotherapeutic agent and rescuing patients with NAC (n-acetyl-cysteine), which raises GSH levels. Knowing that NAC selectively raises GSH levels in normal cells, they were able to show either improvement or stabilization in more than half the patients [19].

Additional studies have considered the effects of nutritional proteins on cancer-causing chemicals in animals. Researchers undertaking similar experiments in Canada and Australia have subjected rodents to the powerful carcinogen dimethylhydrazine—which causes colonic cancer—and fed them with a variety of proteins [20, 21]. The animals fed undenatured whey protein concentrate which raised GSH levels, show fewer tumors and a reduced tumor load. The scientists have found that this particular protein offered considerable protection to the host.

Glutathione, Cancer, and Aging

It is accepted that the incidence and mortality rates of cancer increase with age [22]. Certain cancers can in fact be considered diseases of aging, most notably prostatic cancer [23]. Specific changes in the aging individual's immune response and biochemical defenses such as antioxidant function render them more susceptible to cancer [24]. The protective effect of GSH diminishes with age. The aging individuals may lose from 20 to 40% of GSH after age sixty-five [25, 26]. This has been integrated into several theories of carcinogenesis in the elderly [27].

Studies show that normal levels of androgens in older men lead to decreased GSH levels in prostatic tissue [28]. These androgens are known to act as oxidative stressors and upset the prooxidant-antioxidant balance. This is believed to be a possible mechanism by which prostatic carcinogenesis develops.

Improved Tolerance to Chemo/Radiotherapy

Historically, the concurrent use of GSH augmentation along with chemotherapy goes back several decades [29]. Gynecologic oncologists at the University of California have treated patients with intravenous GSH along with the standard chemotherapy cisplatin [30]. Higher doses of the chemotherapy are possible, with fewer side effects.

A much larger study was performed at Western General Hospital in Edinburgh, UK [31], in which over one hundred and fifty patients with ovarian cancer were treated with cisplatin along with intravenous GSH and were monitored for side effects, quality of life, and outcome. They were compared to equivalent patients not receiving GSH. The group receiving the intravenous GSH showed a statistically significant improvement in depression, vomiting, hair loss, shortness of breath, concentration, and neurotoxicity, and the lab values measuring kidney function. There is a notable trend toward improved outcome [31].

Alopecia (baldness) associated with chemotherapy certainly is not a life-threatening side-effect of chemotherapy,

but can be extremely distressing to the patient. It can also be an indicator of the damage done to other high turnover cells like those lining the intestine. Researcher Jimenez at the University of Miami and others have demonstrated the ability of NAC to protect patients from the baldness resulting from such common chemotherapy agents as cyclophosphamide [32].

Evidences exist suggesting that GSH-enhancing strategies may improve the efficacy or tolerability of certain chemotherapy agents, including adriamycin, cyclophosphamide, and cisplatin [7, 33-36]. However, a complete understanding of the mechanisms of chemoresistance to therapy must be developed to suggest this strategy across the board [37, 38].

Radiotherapists who have investigated the role of GSH in protecting cells have been able to correlate higher pre-treatment GSH levels with a lower amount of radiation burns suffered afterwards [39]. Pre-treatment or simultaneous treatment with products to raise GSH, consistently demonstrate a better tolerance to therapy [40].

Malnutrition/Wasting

Anti-cancer treatment is often accompanied by cachexia, anorexia, fatigue, and decreased muscular strength. Good nutrition is critical and often includes appropriate dietary supplements [41]. The cancer itself, the anti-cancer treatment and the resulting state of nutritional compromise all decrease intracellular GSH levels [42]. This greatly weakens antioxidant and immune defenses, rendering patients more susceptible to other diseases and opportunistic infections [43]. Wulf Droge has focused on cachexia in cancer, AIDS, sepsis and other pathologies. He has noted the similarities among them, pointing to a common cause—GSH and cysteine depletion [44]. He and others have tested the possibility that GSH-enhancing therapy may slow or halt this process of degeneration [45].

Increased GSH synthesis depends on the intake of cysteine-containing foods [16]. Rich sources of this GSH-precursor are very hard to come by and often are not well tolerated by the patient [46, 47]. Cysteine is available as a free amino acid and may be ingested, but it has toxic qualities and does not effectively raise GSH in humans [48]. The drugs NAC and OTC can raise GSH levels but their effects are short-lived [49]. These pharmaceutical drugs also have little nutritional value. Whey proteins have excellent nutritional value but usually lack biologically active GSH-precursors [50]. The ideal source of dietary cysteine should be natural, nutritional, bioactive, and undenatured [51]. The patented whey protein Immunocal fits these criteria. It is biologically active, sustains elevated GSH levels [52, 53], and has high nutritional value.

In 2007 a multi-centered, double-blinded, placebo controlled clinical trial was carried out in Canada [54]. The objective of the study is to see if a specially-prepared whey protein isolate (Immunocal) could improve quality-of-life

variables in cancer patients receiving chemo/radiotherapy. Outcomes show significant improvement, and a statistically significant improvement in preventing and reversing weight loss (cachexia) is evident. Additionally, an increase in survival is noted. This is an important evidence towards maintaining that GSH augmentation is safe and effective when combined with chemotherapy or radiotherapy.

Conclusion

Patients with higher intracellular GSH levels generally demonstrate better prognosis and experience far fewer chemotherapy side effects. In addition, the cells with higher levels of GSH carry more protection against radiation damage, thereby lessening the side effects of radiotherapy as well. GSH modulation represents a novel approach to the treatment and prevention of cancer. Moreover, the use of GSH augmentation during chemotherapy or radiotherapy shows promise as a complimentary treatment to improve outcome and decrease side effects of therapy. Oral forms of GSH do little to raise intracellular GSH levels. Intravenous GSH has proven benefits. Pharmacological GSH precursors such as NAC have been demonstrated to be efficacious, but provide no nutritive value. Specially prepared undenatured whey protein isolate has the great advantage of delivering a high biological value protein and at the same time serve as a rich source of GSH precursors. This may offer the clinicians an opportunity for dietary intervention that goes beyond just nutritional support.

Conflict of Interests

The author provides medical consultation to Immunotec Research.

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