Clinical Observation of a Novel, Complementary, Immunotherapeutic Approach based on Ketogenic Diet, Chondroitin Sulfate, Vitamin D₃, Oleic Acid and a Fermented Milk and Colostrum Product

Michael Schwalb, Margit Taubmann, Steve Hines, Heinz Reinwald and Marco Ruggiero

Innere Medizin Praxis, Leverkusen, Germany
Naturheilzentrum Praxis, Bayreuth, Germany
Hope Wellness Center, San Angelo, Texas, USA
dr. reinwald healthcare, Schwarzenbruck, Germany

Abstract: Here we describe the results of a novel type of complementary immunotherapy of cancer that is based on a combination of ketogenic diet, administration of an emulsion made of chondroitin sulfate, vitamin D₃ and oleic acid and of a fermented milk and colostrum product. The results here reported are consistent with current knowledge concerning the biological and clinical effects of each one of the elements used in the approach described in this study. Based on our results, we suggest that, among the different approaches to the complementary immunotherapy of cancer, those strategies based on ad-hoc formulated nutritional plans and on food supplements that stimulate the immune system and fight inflammation appear to be most promising. Thus, these approaches are characterized by inherent low toxicity and the possibility to use them in conjunction with conventional anti-cancer therapies targeting cancer cells such as radiation or chemotherapies.

Keywords: Chondroitin Sulfate, Cancer, Ketogenic Diet, Colostrum

Introduction

Immunotherapy of cancer has gained a great deal of attention in recent years up to the point that the Editors of the journal “Science” have chosen cancer immunotherapy as “Breakthrough of the Year for 2013” defining this as “a strategy that harnesses the body's immune system to combat tumors” (Science. 2013 Dec 20; 342 (6165): 1432-3). Although the term “immunotherapy” encompasses several strategies that may significantly differ from each other, the common denominator is to target the immune system rather than the tumor itself. This approach is based on the rationale that cancer cells are able to escape immune surveillance because of the typically immunosuppressive tumor microenvironment (Mohme et al., 2016) and, in doing so, they take advantage of the unresolved chronic inflammation that is present in all stages of cancer development. Thus, inflammation at the level of the tumor microenvironment and at the systemic level as cancer progresses, is one of the ubiquitous features of cancer (Pesic and Greten, 2016).

Because of this, among the different approaches to the immunotherapy of cancer, those strategies based on ad-hoc formulated nutritional plans and on food supplements that stimulate the immune system and fight inflammation appear to be most promising. Thus, these approaches are characterized by inherent low toxicity and by the possibility to use them in conjunction with conventional anti-cancer therapies targeting cancer cells such as radiation or chemotherapies.

In this clinical case report, we describe the effects of a novel type of complementary immunotherapy of cancer that is based on a combination of ketogenic diet, administration of an emulsion made of chondroitin sulfate, vitamin D₃ and oleic acid and of a fermented milk and colostrum product.

The role of ketogenic diets in cancer has been known for decades and there exists strong evidence supporting the concept that ketogenic diets may be safely used as
ajdant therapies in conjunction with conventional radiation and chemotherapies (Allen et al., 2014). Although the historical rationale to implement ketogenic diets in cancer was to deprive cancer cells of their main source of energy, glucose, diets that are characterized by very low carbohydrate consumption show other properties that are useful in the integrated management of cancer. Thus, they reduce the synthesis de novo of a second messenger deriving from glycolysis, diacylglycerol, that is responsible for increased resistance to the killing effects of ionizing radiations (Chiarugi et al., 1989; Ruggiero et al., 1992). It can be hypothesized that decreased synthesis of diacylglycerol may be responsible for the increased sensitivity to the therapeutic effects of radiation therapy that has been observed with the implementation of ketogenic diets (Klement and Champ, 2014). In addition, it has been recently demonstrated that ketone bodies have anti-inflammatory, pro-immunogenic properties that are quite relevant in the context of an integrated immunotherapeutic approach to cancer and other diseases associated with chronic inflammation and immunodeficiency (Youm et al., 2015).

In this study we describe clinical cases where the ketogenic diet was integrated with supplements aimed at stimulating the immune system at the same time decreasing inflammation. To this end, we used an emulsion composed of supplements endowed with immune-stimulatory, anti-cancer and anti-inflammatory properties. These supplements are chondroitin sulfate, vitamin D3 and oleic acid.

The rationale for choosing chondroitin sulfate lays in the observation that this glycosaminoglycan is known to negatively regulate cancer cell signaling (Willis and Klüppel, 2014) and to enhance the anti-tumor activity of conventional chemotherapeutics (Ferro et al., 2012). Recent experimental evidence demonstrated that sulfated motifs of chondroitin sulfate are also able to inhibit triple negative breast cancer (Poh et al., 2015). In addition, chondroitin sulfate is a powerful anti-inflammatory agent (Vallières and du Souich, 2010) with known immune-stimulating properties. Thus, chondroitin sulfate stimulates macrophages with the resulting production of nitric oxide, a molecule known to kill cancer cells (Sharma and Chakrapani, 2014), without inducing the production of pro-inflammatory cytokines (Wrenshall et al., 1999).

Vitamin D3 was chosen for two main reasons: one is that a known side effect of ketogenic diets is vitamin D3 deficiency, an occurrence that was first observed in children subjected to such a diet to control epilepsy (Hahn et al., 1979; Bergqvist et al., 2007). The other reason is that vitamin D3 is known to have anti-cancer and anti-inflammatory properties (Ness et al., 2015). Thus, vitamin D3 regulates the cell cycle, induces apoptosis of cancer cells, promotes cell differentiation and works as a natural anti-inflammatory agent within the tumor microenvironment (Díaz et al., 2015).

The rationale for choosing oleic acid, that is the most represented fatty acid of olive oil, lays in the century old observation that olive oil is a powerful anti-cancer agent up to the point that a recent article poses the rhetorical question: “Giacomo Castelvetro’s salads. Anti-HER2 oncogene nutraceuticals since the 17th century?” (Colomer et al., 2008). In addition, mono- and poly-unsaturated fatty acids such as oleic acid significantly decrease the affinity of vitamin D3 for its binding protein, thus increasing the bioavailability of vitamin D3 (Bouillon et al., 1992).

Therefore, the concomitant presence of oleic acid and vitamin D3 in an emulsion also containing chondroitin sulfate may show overall synergistic effects that may be higher than the sum of the anti-cancer and anti-inflammatory properties of each individual component taken singularly.

Finally, the rationale to use a fermented milk and colostrum product lays in the observation that such products are known to enhance the immune system, reduce the risk of certain cancers and decrease systemic inflammation thus synergizing with the effects of the ketogenic diet and of the emulsion of chondroitin sulfate, vitamin D3 and oleic acid quoted above (Khani et al., 2012; Falasca et al., 2015).

Patients and Methods

Methodological Approach

The nutritional-immunotherapeutic approach described in the Introduction is currently implemented in a number of Clinics, mainly in Europe and it is tailored to the individual situation of each patient. Here we present four cases observed in Germany by Drs. Schwalb, M.D. and Taubmann, N.D. A fifth case, patient 5, was reported to Dr. Reinwald. A sixth case, patient 6, was observed by Dr. Hines, N.D., N.E.

It is important to notice that the approaches aimed at strengthening the immune system have to be considered complementary and not alternative to other anti-cancer therapeutic procedures.

We are very well aware that the cases reported here have to be considered anecdotal because of their heterogeneity and small number. It is worth noticing, however, that a study on the evaluation of clinical practice re-evaluates the importance of individual cases in determining the effectiveness of clinical procedures (Nunn, 2011) and, according to Cox, cases such as those reported here “expand expertise, are the unit of clinical work, provide a frame-work for complex details and explain decisions” (Cox, 2001). We chose to report single cases rather than statistics following the indication of Aronson, according to whom the description of single
cases generates and tests hypotheses, elucidate mechanisms and remind or educate (Aronson, 2005).

Patients were treated in compliance with national rules and regulations. Ultrasound determinations, whenever possible, were performed by the Therapists treating the patients. Blood analyses were performed by European certified laboratories. Determination of serum α-N-acetylgalactosaminidase, an enzyme also known as Nagalase, was performed by the European Laboratory of Nutrients (The Netherlands). The original clinical records are conserved in the offices of the Therapists. Descriptions of the clinical cases are reported as close as possible to the originals notes of the Therapists, with minimal grammar and spelling corrections for the sake of clarity and consistency throughout the text.

Nutritional Approach

Patients were invited to follow a diet very low in carbohydrates and rich in fats endowed with anti-inflammatory properties such as extra-virgin olive oil and coconut oil. Since most patients presented with advanced cancer and were at risk of entering the cachexia-anorexia syndrome, their diet was supplemented with a specific amino acid formula which provides an anabolic value close to 99% and, therefore, releases less than 1% of nitrogen waste (ammonia) or energy compared to, for example, formulas containing whey or soy proteins which provide only 16-17% anabolic building blocks and release up to 84% of nitrogen waste and energy (mostly glucose) while being catabolized. As the amino acids in the special formula do not need peptidases to be digested they could be used also in patients with pancreatic cancer to prevent cachexia. The formula was manufactured by the company “dr. reinwald healthcare” (Germany).

The fermented milk and colostrum product consumed by the patients described in this study was produced in Switzerland by the company “Silver Spring”; the immune-stimulating properties of this particular formulation have been described elsewhere (Pacini et al., 2011). The typical daily dose was about 120 mL.

Under the responsibility of the Therapists, this fermented milk product was also administered under the form of enema. Thus, it is well known that probiotics administered by enemas reduce the inflammatory status in experimental colitis (Souza et al., 2007) and rectal administration of lactobacilli in children with active distal ulcerative colitis effective in reducing mucosal inflammation and changing mucosal expression levels of cytokines involved in the mechanisms of inflammatory bowel disease (Oliva et al., 2011). In addition, it has been recently demonstrated that the off-label use of milk and molasses enemas is safe and effective in treating constipation with negligible side effects (Vilke et al., 2015).

Supplements

All the patients described in this report were administered the emulsion of chondroitin sulfate, vitamin D3 and oleic acid quoted in the Introduction. Such an emulsion is manufactured in Germany by “dr. reinwald healthcare” and it is classified and registered as a food supplement since it is composed by well-known supplements that have been in use for decades. Although supplements are usually intended to be administered through the oral route, according to national rules and regulations and under the direct responsibility of the Therapist, they can also be administered through the parenteral route. Thus, the emulsion quoted above was administered orally or parenterally according to the clinical judgment of the Therapist in each individual case.

Other supplements used in the patients described in this study were: Vitamin D3 (10,000-20,000 I.U. per day), curcumin, omega-3, ubiquinol, arginine, multivitamins and a low-molecular weight pectin preparation. This latter product was provided for by “dr. reinwald healthcare” whereas all the other supplements were obtained from local pharmacies and supplement stores. The rationale for the use of low-molecular weight pectin lays in the observation that pectin effectively inhibits the growth and metastasis of gastrointestinal cancer cells (Wang et al., 2016). In addition, pectin is effective at removing toxicants; a study published in 2008, demonstrated that oral administration of pectin was effective at lowering lead toxicity in the blood of children who showed a dramatic decrease in blood serum levels of lead and a dramatic increase in 24 h urine collection with no observed adverse effects (Zhao et al., 2008).

Finally, it should be noticed that each patient followed specific therapeutic regimens consistent with their co-morbidities such as, for example, hypertension or hypothyroidism.

Results

Patient 1

A 70-year old lady was diagnosed with ovarian cancer with multiple metastases in the liver and the peritoneum. Before coming to the attention of the Therapist, she had been treated with multiple cycles of conventional chemotherapy that resulted in reduction of the size of the peritoneal metastases, but were ineffective against the hepatic metastases. The patient had developed severe neuropathy possibly as a consequence of chemotherapy and she could not walk for more than ten meters due to extreme pain and fatigue. The patient had been labeled “incurable” and she had been advised to prepare for the inevitable outcome. The patient came to the attention of the Therapist in such a depressing context and she was treated with the nutritional-
immunotherapeutic approach described in the preceding sections; after about five weeks of treatment, a Positron Emission Tomography (PET) scan did not evidence any appreciable liver metastasis. Blood analyses evidenced elevated percentage of circulating monocytes (8.1%). Normal values: 3-10%, thus supporting the hypothesis that the integrated approach described above stimulated the immune system with particular reference to the monocyte-macrophage arm of immunity. Activation of macrophages following the subcutaneous administration of the emulsion described above was also confirmed by color-doppler ultrasonography following the technique that one of us had described in 2014 (Ruggiero et al., 2014). Most interesting was the decrease of Transketolase-Like 1 (TKTL1) score. Thus, TKTL1 plays a crucial role in ovarian cancer metabolism and its expression predicts poor prognosis (Krockenberger et al., 2010); therefore, decrease in the expression of TKTL1 may be interpreted as sign of decreased aggressiveness of the cancer itself. It should be noticed, however, that TKTL1 expression is not unique for ovarian cancers and it appears that TKTL1 belongs to a group of metabolic genes involved in the glycolytic pathway that is significantly up-regulated in a variety of tumor cells in cancer patients and plays active roles in tumor progression (Furuta et al., 2010). The cumulative TKTL1 score after five weeks of treatment was 125 that is very close to normal values (normal value: less than 119). Also the Apo10 score was decreased, thus confirming the effectiveness of the immunotherapeutic approach from another point of view. Thus, Apo10 is a marker of abnormal apoptosis and proliferation and it represents an independent marker for poor survival for certain carcinomas (Grimm et al., 2013). Consistent with these observations, it has been recently proposed that overcoming drug resistance of Apo10-positive cells in precursor lesions and tumors by natural compounds may act as sensitizers for apoptosis or could be useful for chemoprevention (Grimm et al., 2015). The cumulative Apo10 score after treatment was 149 (normal value: less than 130).

**Patient 2**

A 63-year old man was diagnosed with prostate adenocarcinoma, osteoporosis and esophagitis. The patient had previously been treated with radiation therapy. Magnetic Resonance Imaging (MRI) showed residual tumor lesion. After about four weeks of treatment with the nutritional-immunotherapeutic approach described in the previous sections, Prostate-Specific Antigen (PSA) was significantly decreased from 95 to 0.8 ng mL\(^{-1}\), i.e., the tumor marker had returned to normal values. It is worth noticing that while this patient was undergoing the approach described above, he also received for three times subcutaneous anti-androgen treatment from the Department of Urology of the University of Bochum, Germany. Interestingly, the dramatic drop of PSA from 95 to 0.8 ng mL\(^{-1}\) occurred after the first administration of anti-androgens; the patient refers that such an abrupt decrease puzzled the Oncologists who were treating him since, according to the patient’s story, this was the first time that they had observed such an occurrence. Imaging studies showed significant reduction of the tumor mass that appeared encapsulated with no metabolic activity. The percentage of circulating monocytes was close to the highest normal values (9.2%. Normal value: 3-10%) and activation of macrophages following subcutaneous administration of the emulsion described above was confirmed by color-doppler ultrasonography. Cumulative TKTL1 and Apo10 scores were decreased and, at the end of the treatment, both scores were within the normal values (TKTL1: 115, Apo10: 112).

**Patient 3**

A 66-year old lady was diagnosed with mammary adenocarcinoma, cholelithiasis, colitis and atrial fibrillation. At the time of presentation the tumor measured 0.4 cubic centimeters in volume. Bearing in mind that measurements taken on ultrasonographic images may be affected by a number of variables, preliminary evidence appears to indicate that, three weeks after implementation of the nutritional-immunotherapeutic approach described above, the tumor measured 0.1 cubic centimeters with a reduction of 75% of volume. Also in this case the Therapists observed normalization of the cumulative Apo10 score (value: 123) that was consistent with the observed reduction in tumor size.

**Patient 4**

A 55-year old man was diagnosed with recurrences of adenocarcinoma and adenosarcoma of the esophagus with lung metastases; such recurrences had occurred after a previous surgical intervention targeting these lesions. Also in this case, the patient had been labeled "incurable". After about eight months of implementation of the nutritional-immunotherapeutic treatment described above, the local lesions appear stable and encapsulated with no signs of progression. A Computed Tomography (CT) scan of the thorax performed after about eight months, did not show lesions as if the metastases were no longer detectable. The general conditions of the patients were significantly improved up to the point that the Percutaneous Endoscopic Gastrostomy (PEG) tube was removed as no longer necessary. The patient reported that the Specialists at the University of Düsseldorf, Germany, where these latter procedures were performed, were utterly puzzled by the unexpected positive outcome. Thus, it is well known that the prognosis for esophagus cancer is quite poor with most patients dying within the first year of diagnosis (Polednak, 2003).
Patient 5

A 59-year old man was diagnosed one year earlier with pulmonary nodule of unknown origin. The patient was recommended to undergo surgical excision of the nodule but he preferred to decline such a recommendation and he opted for a multitude of nutritional-complementary approaches which included, among others, low-dose naltrexone, coffee enemas, quercetin, multivitamins, oregano oil, minerals. The patient assumed specific drugs for the following comorbidities; hypertension, left ventricular hypertrophy, hypothyroidism. Tumor markers such as Carcinoembryonic Antigen (CEA), Prostate Specific Antigen (PSA), CA 19-9, CA 27-29 and CA 15-3 were within the normal limits. An interesting laboratory abnormality was represented by level of the serum enzyme Nagalase that was significantly elevated when the patient decided to implement the nutritional-immunotherapeutic approach described in this study. Thus, determination of serum Nagalase resulted in 3.10 Units (expressed as nmol/min/mg) that was well above the indicated reference range of 0.32-0.95 Units. It is interesting to notice that Nagalase may represent at the same time a tumor marker, a marker of inflammation and a marker of bacterial infection. Thus, Taniguchi et al. (1981) demonstrated that squamous cell carcinomas showed increased expression of this enzyme (Taniguchi et al., 1981), whereas Caines et al. (2008) demonstrated that the enzyme is an important virulence factor for Streptococcus Pneumoniae infections (Caines et al., 2008). The patient repeated Nagalase determination about six months after having implemented the approach described above and the results, from the same European laboratory, showed a very significant decrease of the enzyme that approached the normal values (1.34 Units). These results seem to indicate that the immunotherapeutic approach adopted by the patient was effective in decreasing the level of serum Nagalase in a manner consistent with what previously reported for other types of cancer (Thyer et al., 2013).

Patient 5

A fortuitous misunderstanding. Report by Dr. Hines. “In April 2016, we had an interesting situation occur at our treatment facility. A woman, age 73, came to us suffering with epigastric pain, nausea, vomiting and pitting edema in both feet. Her diagnosis was cholangiocarcinoma. Her oncologist stated she was not a candidate for surgery and did not offer any treatment or hope for recovery. The tumor measured 5×6.5 cm, involving the common bile duct. We recommended the patient order 3 vials of the emulsion of chondroitin sulfate, vitamin D3 and oleic acid quoted in the Introduction. She was instructed to take 0.5 cc once daily for 5 days, then take 2 days off. One week later, she returned to our clinic for her scheduled intravenous treatments. When she arrived, I asked her about her epigastric pain, nausea, vomiting and pitting edema. Her answer: No pain, no nausea, no vomiting and only a minor edema in the feet. I was quite surprised at this. When I asked her how much product she was taking, she said she had finished all 3 vials the previous week. The 3 ampoules she had should have lasted for at least a few months, but she had already taken them all in one week! She had misunderstood my dosing recommendations and had taken 1 ampoule daily for 3 days in a row sublingually. Heroic doses to say the least. Now, 6 months later, she still feels just fine and is living a normal life.”

Discussion

The efficacy of chondroitin sulfate and vitamin D3 in cancer is acknowledged not only by the scientific literature quoted in the Introduction but also by the prestigious Mayo Clinic of the United States of America in the section where clinical evidences for different supplements are reported. In the list of the uses for chondroitin sulfate based on tradition or scientific theories listed by the Mayo Clinic, the following uses in cancer can be found: “breast cancer, colorectal cancer, lung cancer, neuroblastoma” (http://www.mayoclinic.org/drugs-supplements/chondroitin-sulfate/evidence/hrb-20058926). Likewise, in the section of the Mayo Clinic pertaining to vitamin D3, the following statement can be found: “Many studies have looked at the effects of vitamin D on cancer. Positive results have been reported with the use of vitamin D alone or with calcium. Vitamin D intake with or without calcium has been studied for colorectal, cervical, breast and prostate cancer. A reduced risk of colorectal cancer has been shown with vitamin D supplementation. …”

The preliminary clinical observations reported in this study suggest that an emulsion of chondroitin sulfate, vitamin D3 and oleic acid administered in the context of an integrated approach encompassing the implementation of ketogenic diet, the administration of probiotic fermented milk and colostrum, ketogenic amino acids, vitamins and pectins, seems to be helpful in the complementary immunotherapeutic treatment of a variety of cancers at different stages of progression. Since this is an open-label, non-controlled, retrospective analysis of heterogeneous clinical data, however, caution must be employed in drawing a cause-effect relationship between treatment and clinical outcome. This is particularly true considering the limited number of cases reported in this study, their heterogeneity and the limited time of observation. In addition, even though some of the approaches described in this article, such as the ketogenic diet or the use of supplements, may be implemented without medical prescription in some countries, it is essential that the
information presented in this study is not construed as medical advice and we always recommend that patients affected by diseases are supervised by competent Therapists even when only nutrition is concerned.

Conclusion

Bearing the limitations of this study in mind, the results here reported are nevertheless consistent with current knowledge concerning the biological and clinical effects of each one of the elements used in the approach described in this article. For example, an old study published more than thirty years ago describing results of the administration of bovine cartilage, whose active component is chondroitin sulfate, states: “Oral and subcutaneous administration of specific preparations of bovine tracheal cartilage rings (Catrix), a nontoxic agent, has resulted in a high response rate in 31 cases of a variety of clinical malignancies (response rate 90%, 61% complete). The demonstrated responders include present therapeutic disasters such as glioblastoma multiforme and cancers of the pancreas and lung. Other types which were treated with success included cancers of the ovary, rectum, prostate, cervix, thyroid and an inoperable squamous cancer of the nose” (Prudden, 1985).

The study concludes with the words: “This wide range of Catrix efficacy now invites investigation by others to confirm the effectiveness of the material and to isolate the molecular entities responsible for these unexpectedly favorable results”. We feel that the results reported in our study not only confirm these old observations, but also move in the direction of fulfilling the request “to isolate the molecular entities responsible for these unexpectedly favorable results”.

Author’s Contributions

Michael Schwalb: Treated four of the patients described in this study.
Margit Taubmann: Assisted Dr. Schwalb in the treatment of the patients and in the collection and organization of data. Drs. Schwalb and Taubmann are responsible for the accuracy of the data reported in this study.
Steve Hines: Reported the observation concerning patient 6.
Heinz Reinwald: Assisted in the organization and in the interpretation of the data and he also provided technical advice on the use of some of the supplements described in this study. He also collected the story of patient 5.
Marco Ruggiero: Wrote the first draft of this paper and provided critical input and assisted in revising and improving the paper. He had no type of involvement in the treatment of patients.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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