Jefferson | Myrna Brind Center of Integrative Medicine

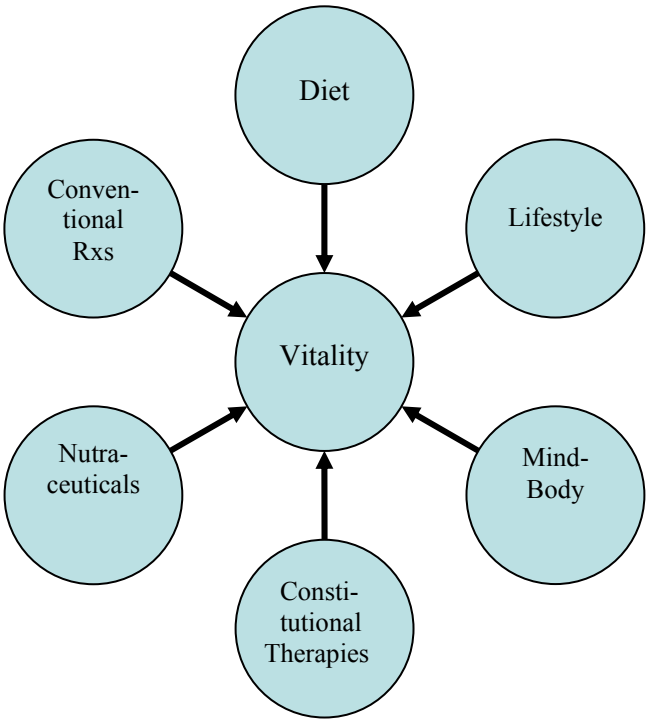
Integrative Medicine and Cancer: Treatment Strategies

Preface

Physicians at the Jefferson Myrna Brind Center of Integrative Medicine (JMBCIM) have been actively treating cancer patients since its opening in 1998. Our treatment approach reflects fundamental principles of integrative medicine and has been enriched through ongoing conversation and exchange with conventional colleagues. As a result, JMBCIM is an active member of Jefferson's NCI designated Kimmel Cancer Center.

The following sections feature **biological therapies** employed in integrative cancer treatment. These include the use of nutraceuticals (micronutrients and botanical medicines) as well as selected pharmacological agents. However, we want to preface this discussion with a brief summary of our overall approach to the cancer patient.

Our core approach to treating cancer is to care for each individual patient, and support his or her vitality in a comprehensive way. Nutrition, lifestyle change, mind-body skills, constitutional treatments, and psychospiritual support are all essential features of our program. Graphically this can be represented by the following figure:



Thomas Jefferson University

Thomas Jefferson University Hospital

Jefferson Health System

Diet. We promote dietary strategies that are generally health promoting: phytonutrient rich, anti-inflammatory, and low-glycemic. We eliminate food allergies and intolerances. We direct patients to learn more about therapeutic diets such as macrobiotics and raw-foods.

Lifestyle. We counsel patients to examine their lifestyle and make necessary changes to support healing. We emphasize healthy rhythms of activity and rest.

Mind-body therapies and psychospiritual support. Patients are encouraged to cultivate self-regulation through mindfulness-based stress reduction classes or tutorials. We refer frequently to health psychologists and other mind-body practitioners for emotional support and creative self-expression.

Constitutional therapies. Many complementary therapies treat a patient's overall constitution, bringing greater balance, harmony, integrity and resilience to the individual's body-mind-spirit ecology. At our Center they include: acupuncture and Traditional Chinese Medicine, homeopathy, massage therapy, Anthroposophical medicine, and Western botanical medicine.

Nutraceuticals and other biological agents. The following sections describe their use in detail.

Core Components of Use of Biological Agents in Integrative Oncology.

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C. **References: Guiding Principles**

A. Historical Considerations

The last two decades of the twentieth century saw the development of the field of integrative medicine. This discipline developed out of a core of basic needs and opportunities:

1. Important gaps in the conventional approach to health and illness have been acknowledged. The value of integrating complementary therapies to fill some of these gaps is increasingly recognized.

2. There is interest to extend past conventional evidence boundaries, such as randomized, double blind studies. Patients with illnesses inadequately addressed by conventional treatments have become willing and interested in exploring treatment methods not as strongly validated by these criteria, but likely to be safe. Many of these treatments involve natural substances, such as herbs, that have a long pattern of historical use in traditional medical approaches from other cultures, such as Traditional Chinese Medicine, Ayurveda, and the folk medicines of indigenous peoples.

3. Patients want to share responsibility and decision making with their health care practitioners for treatment approaches that they can help control and choose. Diet, exercise, mind-body methods, and the use of readily available, appropriately regulated, and apparently safe substances, such as vitamins, minerals and herbs, became very attractive and widely used.

Historically, practitioners of integrative medicine have tended to address particular types of medical situations. These include (a) preventive medicine, (b) illnesses with a self-limiting course, such as viral and mild bacterial infections like otitis media, and (c) illnesses and symptoms where conventional diagnostic and treatment options are very limited. These latter illnesses are extremely prevalent, and include chronic fatigue, fibromyalgia and other chronic pain conditions, irritable bowel, menstrual dysfunction and other "functional" illnesses, and environmental and food allergies.

Most patients with malignancies, particularly in situations where conventional options are limited and potentially more toxic, also search for other treatment options. There have been few "alternative" approaches to cancer treatment that had any level of scientific validity, and treatments were either taken from traditional, historical usage, or their effects were described in quasi-scientific terms such as their ability to "strengthen the immune system."

However, two interrelated developments have led to the present practice of "Integrative Oncology," which is more scientifically based, and can with justification be described as truly integrative with, as opposed to "alternative" to conventional. The first of these developments has been the considerable scientific interest in studying natural substances, such as herbs and vitamins, as well as documenting the effects of psychological processes like meditation. The second development has been the deepening scientific understanding of malignancies, leading to the growing understanding of processes such as signal transduction, cellular transformation, and the subsequent development of targeted therapies. As science has begun to unveil the biological basis of malignant processes like angiogenesis and apoptosis, it has also been discovered that many natural substances have effects on these processes. As an example, a substance such as genistein (an isoflavone present in soy foods) has the ability to act as a weak estrogen agonist, as well as down-regulating various signal transduction pathways (such as NFkB) which are commonly up-regulated in malignant conditions (1,2). These are obvious biological attributes that can be of potential importance in the treatment of malignancies. Another of many examples, is that

Vitamins A and D have been shown to have the effect (by coupling to nuclear receptors which subsequently effect specific genes) of stimulating normal cellular differentiation processes in cancer cells (3,4).

There is a considerable scientific base describing the effect of many of these natural substances in various research settings, including in vitro, in vivo, and animal studies. There is also a small, but growing body of literature describing their effects in relevant clinical situations. Vitamin D has received considerable attention with it's multiple anti-cancer effects (an increase in G_0/G_1 arrest of cellular reproduction, induction of apoptosis and differentiation, and modulation of expression of growth factor receptors, as well as important effects on cell differentiation) (3). The clinical use of Vitamin D in cancer raises concern regarding adverse reactions when high doses are used (such as hypercalcemia), therefore there continues to be great interest in developing vitamin D analogs, as well as different dosing regimens. For example, clinical studies on patients with hormone resistant prostate cancer [see Integrative Approach to Prostate Cancer] have compared the use of docetaxol with or without high weekly doses of calcitriol (1-25 OH Vitamin D), with encouraging results and minimal toxicity. (5,6). The investigation of vitamins, herbs and related substances in these settings is growing and offers considerable promise.

The scientific basis for the use of these substances and methods, however, remains quite limited and of variable strength, depending on which substances are being used. The ethical judgment regarding the use of these incompletely validated methods is therefore open to debate. There are some circumstances where the physician should clearly be very reluctant to introduce them into the treatment protocol. These are clinical situations when the degree of success of the conventional approach is very high, and we would want to limit any intervention that might adversely impact this success. On the other side, there are those situations, unfortunately too common, where the conventional treatment options are minimal, non existent, or potentially very toxic. The choice to consider a treatment that has some rational chance of benefit and is very likely non toxic may be more justified. There are innumerable clinical situations that fall in between these two extremes.

In addition to the potential efficacy against the tumor itself, there are also considerations regarding ameliorating the adverse effects of many conventional treatments. Some treatments appear clearly warranted even if minimally studied, such as the use of massage and relaxation therapy in conjunction with surgery. Others are more controversial, such as the use of high doses of antioxidants concurrent with patients receiving chemotherapy or radiation therapy. There is some theoretical basis to suspect that antioxidants, though they might limit adverse reactions to chemotherapy or radiation therapy, might also limit their effectiveness. Clinical studies though, are mixed in confirming these theoretical concerns (7,8,9,10). These decisions, from an ethical perspective, require choices to be made from the practitioner and informed patient.

With the above as a background, here is described a generic approach of the integrative physician to integrative oncology (particularly as practiced at the Jefferson Myrna Brind Center for Integrative Medicine at Thomas Jefferson University Hospital in Philadelphia). More detailed discussions on specific cancer types, as well as specific treatments, follow in later sections.

B. Guiding Principles

B-1. Synergism

Most malignancies appear to be very complex, with multiple biological factors supporting proliferation, local and metastatic spread. These include processes such as growth factor stimulation, resistance to apoptosis, a local chronic inflammatory milieu, breakdown of local, limiting extracellular tissue, resistance to immune recognition and destruction, and enhanced angiogenesis. Conventional treatment approaches have responded to this complexity with treatments that employ multiple agents with different modes of action. With the advent of targeted therapy, new agents have begun to be combined with older treatment protocols. While the targeted therapy might address specific growth factors, or the process of angiogenesis, the older chemotherapeutic agents most often affect the cell cycle, by blocking certain key steps. It has been recognized that if only one door is blocked, cancer cells will often escape through another exit that hasn't been addressed. Therefore many escape mechanisms are addressed in the treatment protocol.

The same general approach is employed in integrative oncology, yet more so as it is likely that single interventions are not powerful or effective by themselves, but can develop efficacy when combined with other agents, either natural or conventional. There are numerous studies supporting this synergistic effect (6,7,11,12).

The integrative approach therefore targets various relevant pathophysiological processes (such as resistance to apoptosis, chronic inflammation, angiogenesis) simultaneously. It also commonly uses different agents synergistically to address each of these processes. For instance, when addressing chronic inflammation, a protocol employing marine oils, herbs which are known to inhibit inflammatory pathways, and antioxidants are commonly used together.

Many of these natural substances (as well as some conventional medications), have been shown to have multiple effects, as noted above in describing Vitamin D, and equally applied to other substances. Melatonin has significant antioxidant, cell cycle, proapoptotic, immune modulating, and signal transduction effects (13). Mushroom preparations have a wide range of overlapping capacities (14). Therefore, in using a multiagent protocol, with agents that by themselves have a wide range of effects, we are attempting to target numerous essential pathophysiological processes.

A caveat is that, in our present state of knowledge, we are relatively ignorant of how such agents interact when combined in these ways. The anticipated synergism, while partly studied in specific instances, has not been studied or evaluated in all the complex regimens that are commonly recommended.

B-2. Anti-Inflammation

The milieu surrounding malignant cells has a chronic inflammatory character. Measurement of various proinflammatory substances (such as COX 2 enzymes, proinflammatory prostaglandins, and signaling agents such as NFkB) shows increased concentration (15,16). The presence of inflammation has the effect of promoting cancer growth and spread. Coussens has described: "The protumor actions of inflammatory cells include releasing growth and survival factors, promoting angiogenesis and lymphangiogenesis, stimulating DNA damage, remodeling the extracellular matrix to facilitate invasion, coating tumor cells to make available receptors for disseminating cells via lymphatics and capillaries, and evading host defence mechanisms" (16).

The approach to counter chronic inflammation includes diet, various supplements, and occasionally prescription medications. An anti-inflammatory diet is one which emphasizes omega-3 fatty acids (found especially in fish and to a lesser extent whole grains), and limits arachidonic acid-containing foods (meat and dairy), and includes anti-inflammatory spices such as ginger and turmeric. This dietary approach leads to the formation of anti-inflammatory prostaglandins and eicosanoids. In addition, high antioxidant and flavonoid foods (fruits and vegetables) are favored, whereas toxin producing food preparation processes (processing, additives, deep frying) are discouraged. In practical terms, this whole food diet is rich in varied vegetables and fruits, with an ample amount of fish, especially oily fish like salmon, herring, sardines (and to a lesser degree, because of mercury toxicity concerns, tuna), as well as lower amounts of dairy and especially red meat.

Dietary supplements include (a) fish and flax oils (containing omega-3 fatty acids), (b) anti-inflammatory herbs such as curcumin (curry) and boswellia (frankincense). Antioxidants counter inflammation and include vitamins like C in moderate doses, as well as plants such as grapeseed (containing pycnogenol), and green or red tea concentrates.

Attempts to block multiple inflammatory pathways, such as those involving COX and leukotrienes is encouraged, since if only one pathway is blocked, substances will then use an alternate pathway (17). The supplements mentioned above can have dual COX/LOX inhibitory properties, as opposed to the sole use of pure COX and LOX inhibitors such as celecoxib and zileuton. In highly inflammatory states, these prescription medications may be considered along with the broader but less potent acting supplements (although recent information regarding potential negative cardiovascular consequences with COX-2 inhibitors, albeit incomplete, needs to be strongly considered).

Various lab tests, such as high sensitivity CRP and fibrinogen give general indications of the overall degree of inflammation and can help guide treatment intensity (18,19), although in practice, these measurements are often too non specific. Better lab tests, which would help monitor response to these measures, have not been adequately identified to date.

i. In Depth: Use of Fatty Acids in Malignancies

B-3. Anti-Angiogenesis

It is widely recognized that angiogenesis is an important factor in almost all tumor types, including solid and probably most hematological malignancies. Angiogenesis is a complex process, involving the tumor cell and the microenvironment, as well as vascular endothelial cells. The most successful antiangiogenic treatment would involve many agents that target numerous factors, such as the endothelial cells directly, as well as growth factors produced by the tumor and the microenvironment which stimulate the endothelial cells to form new blood vessels (20,21). There are also suggestions that angiogenesis treatment might potentiate chemotherapy and overcome chemotherapy resistance, by improving medication delivery through normalization of the tumor vasculature (22).

However, there is also the possibility that angiogenesis treatment may diminish the efficacy of chemotherapy because angiogenesis inhibitors might slow the growth of malignant cells, which could interfere with chemotherapeutic agents that target cells which are in an active growth cycle. It is also possible that anti-angiogenic treatment may reduce drug delivery through abnormal, tumor vasculature.

In the real life clinical situation, it is somewhat artificial to characterize the pathophysiological situations of angiogenesis, inflammation and apoptosis as distinct, separate processes, as they are intimately related. Chronic inflammation produces various growth promoting substances that stimulate angiogenesis, and blocking angiogenesis can lead to apoptosis. Therefore the clinical approach to chronic inflammation, as discussed above, can have indirect beneficial effects in limiting angiogenesis.

The integrative medicine approach to angiogenesis involves an attempt to block numerous steps in the process, both directly and indirectly. An agent of considerable interest is ammonium tetrathiomolybdate (TM), which functions primarily as a copper chelating agent, lowering the amount of copper available. As opposed to agents such as anti-VEGF antibodies, TM has multiple and wide ranging effects on angiogenesis. Copper has an important role in many processes that stimulate angiogenesis, including the production and delivery of various growth factors, including VEGF, as well as effecting signaling molecules such as NFkB (23,24).

TM has been studied as a single agent and also in combination with standard agents (25,26,27). There are various cautions and limitations in regard to its use in clinical practice: First, it is considered an unapproved, experimental agent by the FDA. Second, although only a fraction of the cost of approved drugs such as bevacizumab, it is not covered by insurance. Third, the therapeutic window for copper levels is narrow. Reversible myelosuppression may occur should copper levels fall below the target range; this requires careful and frequent monitoring of blood cell counts and ceruloplasmin levels.

Clinicians have reportedly utilized TM in various clinical situations, such as patients with a first recurrence, as well as with more advanced metastatic disease. It has also been used in patients with no measurable disease who are either at high risk for recurrence or have rising tumor markers

Various vitamins, most specifically Vitamin D, Vitamin E (notably Vitamin E succinate) (28,29,30), Vitamin B6 (31,32), and Vitamin C (33), have been demonstrated to have inhibiting effects on angiogenesis. Numerous other natural medications, such as the coriolus mushroom, which is primarily used for its effects on immune function, also have beneficial effects on angiogenesis (34).

a. In Depth: Medicinal Mushrooms

B-4. Antioxidants and Detoxification

The rationale behind the use of antioxidants and detoxifying agents is addressed in two parts. The first section discusses their use when the patient **is not** receiving chemotherapy or radiation therapy. The second section discusses their use when patients **are** receiving these therapies.

Antioxidants and detoxifying agents protect the body against the effects of free radicals and other substances which produce toxic effects, such as xenobiotics. These therapeutic agents have other effects, however, which should be considered. They have beneficial effects on countering inflammation and immunosuppression, deleterious processes which are very prevalent in patients with malignancies (35,36). It is well known that patients with malignancies have an increased level of inflammation and oxidative stress, as well as a deficiency of protective antioxidant and detoxifying substances such as glutathione (37,38). The presence of free radicals can also directly effect DNA and foster further mutations in malignant cells already prone to free radical damage. Other antioxidants, such as Vitamin A, have additional effects, such as promoting normal cell differentiation.

An integrative treatment program involves the use of multiple antioxidants and detoxifying agents, rather than one or two. Various studies looking at antioxidants and cancer have examined the use of only a few agents, and have shown inconclusive or even negative effects (as with synthetic beta-carotene only in the CARET trial)(39). It has subsequently been realized that the particular physiological conditions in this trial led to beta-carotene functioning as a **prooxidant**, and to a depletion of protective detoxifying agents (40). Since the hypothesis in this trial was that malignancies would increase as the level of free radicals increase, it was a **positive** trial, as the particular protocol of beta-carotene administration led to an increase, rather than the expected decrease, of free radicals. This is the opposite of the message that most physicians have gotten from this trial, that the use of isolated antioxidants, particularly beta-carotene, is deleterious. It is inappropriate to extrapolate these negative results to a situation where multiple antioxidants and detoxifying agents were being used simultaneously, such as in a typical integrative treatment protocol. The goal is developing a protocol where the net effect is an **improved** antioxidant status and improved detoxification, the opposite of what occurred in the CARET trial.

An integrative program involves the combined use of micronutrient antioxidants, as found in high potency multivitamins, plant based antioxidants (such as pycnogenol from grape leaves), and substances such as melatonin in supraphysiological doses. Melatonin in particular has been studied in conjunction with conventional treatment protocols. Patients with a range of advanced metastatic solid tumors were treated with chemotherapy with or without melatonin, and the active treatment group was shown to have very significantly decreased toxicity, as well as improved regression and survival rates (41).

The use of antioxidants concurrent with chemotherapy or radiation therapy remains a controversial topic. Most oncologists advise their patients not to use significant doses of antioxidants while receiving these therapies. This recommendation is based on the understanding that certain chemotherapeutic agents, most particularly alkylating agents, tumor antibiotics, and platinum based compounds, as well as radiation therapy, exert some of their cytotoxic effects through the formation of free radicals. It is therefore **theoretically** felt that antioxidants can interfere with these effects. It should be understood though, that there is basically no clinical literature, and a paucity of in vitro studies that support this position. The literature that is available supports the opposite position, that the use of antioxidants decreases potent side effects of chemotherapy and might actually increase the efficacy of chemotherapy and radiation therapy (42). There is, however, one specific detoxifying agent, glutathione, and related substances such as n-acetyl cysteine and lipoic acid, which are very likely to decrease chemotherapy efficacy and promote resistance (43,44). These agents should always be omitted when chemotherapy or radiation therapy is being used. Of interest is that other substances, most notably Vitamin C, leads to depletion of glutathione in cancer cells (45). Numerous studies show synergistic benefit when vitamin C is combined with chemotherapy or radiation therapy (46,47). The mechanism of depleting glutathione in malignant cells may account for this seeming beneficial effect. When Vitamin C, bypassing the limitations of absorption through the gastrointestinal tract, is given in very high doses intravenously, dramatically higher levels are able to be attained, and a **prooxidant effect occurs** (48). The combination of attaining higher blood levels, which are potentially cytotoxic (49), production of free radicals, and depletion of glutathione, suggests the potential that intravenous administration of high doses of Vitamin C augments the effects of chemotherapy and radiation therapy.

The decision to use or omit antioxidants (which as noted above have other beneficial effects on inflammation, immune function and differentiation) when patients are receiving chemotherapy or radiation therapy is therefore a difficult, and ultimately, individual one. In situations where conventional treatment is known to be very effective, we should clearly be very cautious in the use of

antioxidants. In situations where conventional treatment offers little benefit, the use of antioxidants as an active treatment method may be more strongly considered for their palliative, and potentially adjunctive treatment effects. In all the situations in between, the physicians and the patient will need to make their individual decisions.

Although the use of antioxidants with chemo/radiation therapy is controversial, the use of anti-inflammatory substances concurrent with chemo/radiation therapy is widely supported in the literature (50-57). The use of chemotherapy evokes an increased production of the signaling molecule, NFkB, which fosters chemo-resistance. Many anti-inflammatory herbs, such as curcumin and milk thistle, block this production of NFkB, and appear to increase efficacy of numerous chemotherapeutic agents.

B-5. Cellular Re-Differentiation

In general, cells that are less differentiated have a greater tendency to proliferation. This effect is most clearly seen with embryonal cells, and especially stem cells. As cells mature, they become more differentiated into specific cell types, with a consequent significant decrease in proliferative ability. Cancer cells tend to regress to a less differentiated phenotype. Those cells that are the least differentiated tend to show greater malignant properties. This appearance is evident in the pathological description of cancer cells, often described on a range of well differentiated to poorly differentiated or anaplastic. These processes of differentiation are significantly under genetic control.

Vitamins A and D, as well as the class of hypoglycemic agents known as the glitazones effect specific nuclear receptors (RAR, RXR, VDR and PPAR), which induce differentiation. These agents also have other beneficial effects. Vitamin D, for instance, has the ability to (a) induce differentiation, (b) induce apoptosis, (c) induce the activity of the tumor suppressors p21 or p27, (d) inhibit angiogenesis, and (e) inhibit cell migration (56). The use of these agents has been limited by toxicity, such as hypercalcemia with high doses of Vitamin D. There is active research investigating different forms and dosing schedules of these agents (59,60).

Another potential way to conserve efficacy and reduce toxicity is to use these agents together, inducing synergistic effects. This would potentially allow lower doses to be employed. These substances are known to work synergistically (61,62). Studies on single agent efficacy have shown no, or only mild efficacy (63,64). Vitamin D, as calcitriol, given in high weekly oral doses in combination with docetaxel, has shown benefit in prostate cancer patient with androgen independent tumors, compared to historical controls (65). A phase 3, placebo controlled trial on the use of calcitriol with docetaxel has **recently** shown improved results compared to docetaxel alone (66) These differentiating agents have not been studied, however, in a potentially synergistic combination of agents, in the context of an integrated treatment protocol.

These agents have actions in addition to inducing cellular differentiation. Retinoids, such as the forms found in foods and supplements (retinyl ester such as retinyl palmitate), 9 and 13 cis retinoic acid, as well as pharmacological forms such as all trans retinoic acid (ATRA), exert their effects through the transcription of a variety of genes critical to cellular proliferation and differentiation. These vitamins have also been shown to promote apoptosis and cell cycle arrest through degradation of stimulatory proteins. This degradation occurs through the proteosome/ubiquitin pathway (64), known as proteosome inhibition. PPAR agonists have also been shown to have numerous relevant clinical effects besides differentiation, including inhibition of NFkB, proapoptotic, antiproliferative, and antiangiogenetic actions.

A synergistic program of differentiating agents would vary, depending on the specific clinical situation. Short term use would employ much higher doses than ongoing maintenance treatment. Appropriate monitoring of levels of retinol, 25 OH and 1-25 OH Vitamin D, liver enzymes, calcium and glucose is essential.

Potential oxicity, especially with the fat soluble vitamins A and D, are important considerations. The dosages of vitamin A are likely to be very dependent on the length of the course of treatment. Most physicians prescribe Vitamin D in doses far below the optimal range, typically in doses of 400-800 i.u./day. Significant literature suggests that doses as high as 4000 i.u./day are very safe. Nevertheless, high doses can potentially induce hypercalcemia. Therefore monitoring should be regularly performed. It should be noted that most laboratories report normal ranges of Vitamin D which are probably significantly lower than the optimal levels. One should aim for a range of 50-100 ng/ml, or 100-180 mmol/liter. The use of PPAR agonists involves at present mainly prescription medications primarily used for diabetics, the glitazones.

In addition to the synergistic effects noted between these three groups of agents, numerous other substances, including antioxidants and anti-inflammatory agents, have been shown to increase their benefits. Therefore the use of differentiation agents should be combined with the general integrative treatment protocol outlined elsewhere.

a. In Depth: Agents Promoting Cellular Differentiation

B-6. Immune Modulation

"Alternative" approaches to malignancies often base themselves on "stimulating the immune system". As with all such generic statements, the issue is much more complex, and incompletely understood. It is widely thought that there exists an innate immune surveillance system, whereby nascent malignant cells are recognized by the immune system, and destroyed before they have a chance to grow and become established. It is also widely thought that the immune system, if appropriately activated and directed, can be a potent ally in the fight to eradicate already established cancers, or prevent their recurrence once a patient undergoes surgery, chemotherapy or radiation therapy. Conventional attempts to enlist the help of the immune system in the treatment of malignancies have included general stimulation such as occurs with BCG, the use of cytokines such as interferon or interleukin (usually in high doses), monoclonal antibodies such as rituximab, and vaccines. In patients with malignancies, it is recognized that certain deficiencies exist, such as defective maturation of dendritic cells, which are essential for the presentation of the tumor antigens to the immune system (65,67). It is also recognized that other factors, such as the presence of reactive oxygen species, or inflammation, can play a role in the suppression of the immune response, and help the tumor escape the effects of this response (68,69). Investigation in these areas is very active and appears promising.

Various natural substances have direct effects on immune processes. The most well known examples are medicinal mushrooms, which are used very widely in Asia, and mistletoe preparations, which are used widely in Europe. A preparation made from the Coriolus mushroom, called PSK (polysaccharide Krestin) has been shown to positively effect dendritic cell maturation, as well as stimulate NK and LAK function (70,71). Various potentially beneficial immune effects have also been noted with Mistletoe (71,72). These agents have also been studied in clinical settings. Coriolus preparations have been studied in numerous gastrointestinal malignancies, with statistically positive

results (73,74,75). Mistletoe has likewise been studied in various clinical settings, with unclear but potentially beneficial effects (76,77).

In the context of the known immune defects in patients with malignancies, it has become routine in most integrative treatment protocols to include an immune active agent, such as the mushroom or mistletoe preparations discussed above. These treatments are done, as always, in the context of the comprehensive protocol. The inclusion of antioxidants and anti-inflammatory preparations is likely to have further potentially beneficial effects on immune functioning. There are certain caveats and exceptions to the inclusion of these immune active agents. This caveat is particularly true with hematological malignancies. These malignancies, such as lymphomas, typically involve immune active cells, such as B or T lymphocytes. As substances like mushrooms and mistletoe have effects on a multitude of immune active cells and functions, there is the potential concern that the use of these substances could inadvertently stimulate malignant cells.

i In Depth: Medicinal Mushrooms
ii .In Depth: European Mistletoe

B-7. Apoptosis

The induction of apoptosis, or programmed cell death, stands side by side with the inhibition of increased cell proliferation, as a vital therapeutic goal in the treatment of malignancies. Apoptosis is a common final pathway for dying cells, and therefore is effected in multiple ways. Many cancer cells, through the upregulation of the gene BCl-2, resist apoptosis. This resistance has numerous consequences. The resistance to apoptosis allows damaged and mutated cells to survive, and ultimately proliferate. It also prolongs the lifespan of cells, and makes them more likely to develop mutations. It also helps resist the cytotoxic action of various agents, such as chemotherapy. It can change the effect of a cytotoxic agent into one of cytostasis. The normalization of all of the above mentioned functions, such as antiangiogenesis, decreasing inflammation and strengthening immune function, lead to apoptosis. Most chemotherapeutic drugs induce apoptosis. There are, in addition, specific natural substances which have been noted for their ability to induce apoptosis.

Vitamin E succinate has been shown to increase the expression of Fas protein, and decrease PCNA protein on gastric carcinoma cells in a dose dependent manner (78). The presence or absence of these proteins, respectively, is associated with the tendency to apoptosis. Another study showed its effects were related to BCl-2 (79). An in vivo study of immunocompromised mice with malignant mesothelioma being treated with Vitamin E succinate, showed a significant effect on survival (80). There is however, considerable doubt regarding the ability of Vitamin E succinate to survive the proteolytic activity in the GI tract. The above mentioned studies were in cell culture.

Green tea, and polyphenols found in green and red tea such as epigallocatechin gallate (ECGC), have also demonstrated the ability to induce apoptosis (81,82). Direct effects on BCl-2 proteins have been shown (83). There are numerous green an red tea concentrates available commercially which allow the administration of the equivalent amount of ECGC found in 30-45 cups of decaffeinated green tea.

B-8. Tumor Specificity

In addition to the overall approach outlined above, various tumor types, such as hormone sensitive breast and prostate cancer, are approached through substances that address these hormone sensitivities. The relative proliferative stimulation of estrogens can be effected through the use of

indoles, such as diindole methane (84). Various brain tumors have shown sensitivity to boswellic acid, derived from frankincense (85). Different cancers, such as colon and prostate, have demonstrated an enhanced sensitivity to inflammatory factors, and therefore the anti-inflammatory aspect of the general protocol would be emphasized in these tumors. Other tumors, such as indolent lymphomas, have a significant upregulation of BCl-2 proteins and resistance to apoptosis. Therefore proapoptotic agents are emphasized in the overall treatment program. As more is learned about the specific biochemical, signal transduction and molecular aspects of tumor types, and how different natural substances can affect these processes, the treatments can potentially be tailored in a more exact way. In a similar way, as gene profiling of individual tumors progresses, this will allow tumor tailored to the individual patient.

B-9. Summary

The integrative approach to the treatment of malignancies usually involves a multiagent protocol, attempting to address known factors that promote the growth, spread and metastasis of tumors. Numerous agents are typically employed to address inflammation, angiogenesis, and apoptosis. Inflammation, as an example, is often addressed through diet, high doses of omega-3 fatty acids, and herbs such as curcumin and boswellia, which are known to affect COX-1, COX-2 and leukotriene pathways. As in all illnesses, different phases of the illness are treated differently. The treatment of a patient undergoing surgery can be significantly different from one in a watch and wait mode. The level of evidence supporting these treatments is relatively low compared to that available for conventional treatments, although a great deal more literature exists than is generally recognized or acknowledged. The toxicity of these integrative agents is relatively low.

Various controversies exist regarding the use of these incompletely studied agents. One very important consideration is whether antioxidants should be used concurrently with chemotherapy or radiation therapy. In addition to the use of natural substances, other modalities, such as acupuncture and therapeutic massage, are often suggested, and can be of significant benefit in many clinical situations. The basic science literature concerning these substances is substantial, and the presence and experience of clinicians is sufficient, to allow fruitful clinical inquiry and appropriate application as to their potential role in the treatment of patients with malignancies.

B-10. Generic integrative protocol for biological agents in malignancy

Anti-Inflammation

1) Anti-inflammatory diet.
2) Fish Oils containing omega-3 fatty acids – dosage ranges typically from 4-20 grams of a typical fish oil supplement, one capsule of which typically contains about 4-500 mg of EPA and DHA. Some fish oil supplements contain twice the amount of EPA and DHA and dosage should be adjusted accordingly.
3) Curcumin – 1500-3000 mg daily.
4) Boswellia – 900-1800 mg daily
5) COX 2 inhibitors – due to the recent concern of an increase incidence of cardiovascular incidents, especially with high doses, these agents should only be used judiciously and in combination with other agents that block the other inflammatory pathways, such as COX 1 and leukotrienes. It should be noted that recommended herbs above also have inhibiting effects on these other pathways.
6) Leukotriene inhibitors – consider montelukast 10mg/d in more advanced situations, again with the considerations noted about COX 2 inhibition.
7) Consider monitoring of inflammatory markers: high sensitivity CRP, fibrinogen, IL6.

Anti-Angiogenesis

1) Antiinflammatory and antioxidative programs decrease angiogenesis.
2) Experimental agents such as ammonium tetrathiomolybdate may prove beneficial.

Immune Modulation

1) European mistletoe.
2) Mushroom preparations – Coriolus preparations (PSK and PSP) are the most widely studied. Dosages are 1500-3000 mg daily. Other preparations, such as Maitake, Shitake and mixtures are also commonly used. Genistein Complex Polysaccharide, a fermented combination of genistein and ganoderma, combines in a synergistic manner the benefits of isoflavones and mushrooms

Anti-Oxidant and Detoxification.

1) Assess risk/benefit in conjunction with chemotherapy and radiation.
2) High potency multivitamin/mineral supplements – numerous good formulations exist. Use formulations which are iron and copper free. Assure daily intake of selenium 200-400 mcg.
3) Pycnogenol – grape leaf and pine needle preparations contain pycnogenol. (400 mg of pycnogenol/day)
4) Green tea concentrates, decaffeinated – equivalent of 15-45 cups daily, or red tea concentrates (naturally free in caffeine and oxalic acid and low in tannins.
5) N-acetyl cysteine – 1500 mg daily (see also under detoxification)

Promote Apoptosis: effected by all of the above

Re-Differentiation.

1) Vitamin A – blood levels need to be checked at baseline and with extended use.
   Short term use – 100,000-300,000 iu/day, not to exceed 1-2 months
   Medium term use – 40,000-50,000 iu/day, for up to 1 year
   Long term use – 20,000 iu/d, for up to 5 years there is a concern re: osteoporosis
2) Vitamin D. Correct to serum level 25-OH-D of 75 ng/ml.
   Vit D2 or Vit D3 – 1,000 – 6,000 iu/day
   Calcitriol (1-25-OH vit D) - .5mcg/kg weekly
3) Consider the use of insulin sensitizing agents, such as glitazones (Actos or Avandia), especially in overweight patients.

Tissue Specific Agents

1) Breast Cancer:
   Flax seed
   Indole-3-Carbinol or Di-Indole Methane. Adjust dosages by the ratio of 2 OH /16 OH estrogen metabolites
2) Prostate Cancer:
   Genestein Concentrated Polysaccharides
   Lycopene

C. References: Guiding Principles

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