European Review for Medical and Pharmacological Sciences 2023; 27: 10507-10521

Integrative multidisciplinary approaches by the Integrative Medicine Research Group (IMRG): a new frontier in cancer setting

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Abstract. – This conference addresses the topic of integrative, multidisciplinary approaches to cancer settings according to evidence-based medicine. The multidisciplinary approach of the researchers involved characterizes this new and complex scenario. The Integrative Medicine Research Group (IMRG) has always been committed to the activities and dissemination of CAM in cancer patients, focusing on the safety and efficacy of these approaches. Thus, one of the main goals of IMRG is to demonstrate that CAM can support cancer patients during treatment and improve their quality of life and survival. In addition, IMRG's multidisciplinary network is ever vigilant in assessing the risks of interactions between cancer drugs and nutraceuticals. We hope that the integrative medicine approach can be transferred to the level of all chronic diseases, including oncology.

Key Words:
Cancer disease, Patients, Treatment, Medicinal mushrooms, Integrative oncology, Interactions, Physical activity.

Introduction

According to the English literature and the National Center Institute of USA for Complementary and Integrative Health (NCCIH)[1], integrative multidisciplinary medicine combines traditional medicine (TM) with Complementary and Alternative Medicine (CAM) practices. The use of CAM has demonstrated its safety and efficacy in conjunction with traditional cancer treatments[2-10]. This innovative approach involving also the disease's mental and spiritual aspects includes a wide range of practices and products conventionally divided into five categories (Table I).

The use of CAM remedies among cancer patients is widespread, and the patient often omits this information to the oncologist. This behavior may represent a risk for the clinical management of the cancer patient[2-4].

The integrative approaches could represent a valid strategy of treatment as long as properly used. Several CAMs can be considered safe and efficacious, but their use requires extensive and accurate knowledge of both the specific cancer characteristics and the CAMs mechanisms.

CAM therapeutic properties are mainly supportive, although they have been demonstrated to improve patients' quality of life (QoL) and survival.

The appropriateness of the CAMs' prescriptions implies several factors, such as the deep knowledge of their synergic activities as well as their safety profile, the continuous and adequate training of the physicians and healthcare personnel involved in patient care, and the proper information to patients in order to avoid self-prescriptions of CAMs.

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Table I. CAM categories according to NCCIH. The National Center for Complementary and Integrative Health divides CAMs into five categories or domains on the basis of their nature and application.

	Mind-Body therapies	Biologically based practices	Manipulative and body-based practices	Biofield therapy	Whole medical systems
Meditation	✓				
Biofeedback	✓				
Hypnosis	✓				
Yoga	✓				
Tai Chi	✓				
Vitamins		✓			
Dietary Supplements		✓			
Botanicals		✓			
Herbs		✓			
Special foods or diets		✓			
Massage			✓		
Chiropractic therapy			✓		
Reflexology			✓		
Reiki				✓	
Therapeutic touch				✓	
Ayurvedic medicine					✓
TCM*					✓
Homeopathy					✓
Neuropathic medicine					✓

*TCM: Traditional Chinese Medicine; ✓ Identifies the category to which the CAM belongs.

With this new conference focusing on the management of cancer patients within a multidisciplinary and innovative approach, the Integrative Medicine Research Group (IMRG) aims to raise awareness of the need to promote clinical trials involving the use of integrative medicine in clinical practice and to organize a service for integrative medicine in the national health system.

Oral Session

Risk and Benefits of Concomitant Use of Herbal Products and Anticancer Drugs in Complementary and Alternative Medicine

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Recently, interest in natural products for the treatment of pathologies or health disorders has grown exponentially[10]. Epidemiological data demonstrate that approximately 80% of the world's population is inclined to use traditional phytotherapy for the treatment of minor ailments or for the treatment of non-serious pathologies[1]. Nowadays, numerous herbal medicines used for maintaining well-being are available through various commercial channels. Of these, only a small part is controlled by the health authorities[1,2]. We know that only a small proportion of herbal products are subjected to qualitative, safety, and efficacy analyses[1]. It is indeed a common belief that preparations based on medicinal herbs are essentially harmless and, therefore, used as a form of self-medication. This common practice very often takes place without the knowledge of the attending physician[1,2,5]. Scientific literature shows that there are numerous risks of interactions between herbal products and drugs. Sometimes, these side effects, affecting the gastrointestinal tract or the central nervous system, result from the specific pharmacological-toxicological activity of the product or from its interaction with the drugs taken by the patient[11-13]. Chemotherapy is known to have many side effects, which can occur during the first few cycles of therapy but also as a cumulative effect after several cycles. To reduce the short- and long-term side effects, Complementary and Alternative Medicine (CAM) is a promising option for many patients[2,3,5]. Mainly, CAMs are used to reduce the side effects of che-

motherapy, but also because of the synergistic anti-tumor effect that some extracts have shown and to strengthen the immune system, which plays a key role in tumor development and progression[1-3]. It emerged that the majority of CAM users consider therapies not only effective and safe but also harmless when used in conjunction with cancer treatments[9]. In fact, the concomitant use of herbal medicines with conventional therapies is one of the major concerns of physicians in treating their patients and may lead to unexpected consequences[1-3]. Recent studies[1] highlight the use of herbal products, vitamins, and minerals in conjunction with chemotherapy due to their antioxidant properties, which help prevent side effects and improve quality of life. However, there are documented interactions between some commonly used herbs and chemotherapeutic agents. For example, free radicals produced by the cytotoxic effects of drugs such as anthracyclines, platinum compounds, alkylating agents, bleomycin, and epipodophyllotoxin interact with extracts having antioxidant activity[1,11]. Another example of risk interaction in cancer treatments is the use of St. John's wort (*Hypericum perforatum*) or grapefruit extracts (*Citrus* spp.), which are potent inducers or inhibitors of cytochromes (CYPs), respectively. It is, therefore, clear that concomitant use of these extracts with anticancer drugs metabolized by CYP3A4 is a risk factor for the development of toxicity or treatment failure[1] (Table II). Thus, the use of CAM improves patient outcomes in terms of reducing chemotherapy drug-induced toxicities but requires close evaluation of potential interferences in drug metabolism[14-17] (Table II).

Micotherapy in Cancer Setting: the State of Art

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Mushrooms have been valued worldwide for over a thousand years as food, but also for their medicinal properties. Cumulative evidence from animal models and human studies[18-20] strongly indicates their immunomodulatory, antiallergic, anticholesterol, neuroprotective, and anticancer properties. Several studies[18-20] have evaluated their effects on cancer using *in vitro* and animal models; some studies have tested mushrooms or some specific extracted fractions in phase I, II, or III clinical trials for various diseases, including cancer, and for modulating immunity[18-20]. The most beneficial effects of mushroom supplementation in cancer patients shown in published studies[21-26] are strengthening the immune system[21,22], reducing inflammation[23], modulating oral and gut microbiota[24], reducing side effects of conventional therapies (chemotherapy, radiotherapy, and targeted therapies)[25], reducing the tumor microenvironment[26], and improving quality of life[25] (Figure 1). The anti-cancer effect of medicinal mushrooms could be due to several effects. The first is the modulation and strengthening of the innate immune system, which is mainly carried out by branched beta-glucans. The beta-glucans bind to specific receptors and activate an epigenetic response that enhances immune surveillance. Recently, a new smart way to enhance innate immune defense by beta-glucans has also been revealed, which is called "trained immunity". Trained immunity is a phenomenon based on epigenetic and metabolic changes and reprogramming that leads to an enhanced response of innate immune cells; the cells become capable of developing memory. Beta-glucans can activate trained immunity by reprogramming the innate immune response, epigenetics, and metabolism, providing a novel intervention strategy for both disease prevention and treatment[27]. Another important effect of mushrooms (containing particulate beta-glucans, polyphenols, and other bioactive molecules) is the modulation of the microbiota[24]. The effects on the microbiota are particularly interesting because the microbiota shapes immunity and is involved in maintaining health. However, the composition of the microbiota also affects the efficacy and side effects of chemotherapy and novel targeted immunotherapy, is involved in shaping the tumor microenvironment, and consequently affects cancer progression[28]. Medicinal mushrooms improve the quality of the gut microbiota: they increase the Bacteroides/Firmicutes ratio, reducing inflammation and improving metabolism; they have a bifidogenic effect, promoting the growth of anti-inflammatory and short-chain fatty acid (SCFA)-producing bacteria and increasing the richness and biodiversity of the microbiota. They also support the maintenance and healing of the intestinal barrier[29]. In addition, many research groups have reported that mushroom supplementation can reduce or minimize some undesirable side effects of chemotherapy and radiation therapy, such as nausea and vomiting, asthenia, bone marrow suppression, anemia,

Table II. Interactions between commonly used phytomedicines and antiblastic drugs.

			HERBAL REMEDIES												
			Allium sativum	Boswellia spp.	Camellia sinensis	Citrus spp.	Curcuma longa	Echinacea spp.	Ginkgo biloba	Glycirriza glabra	Hypericum perforatum	Panax spp.	Silybum marianum	Valeriana officinalis	Zingiber officinale
		ENZYMES	CYP2C19 CYP2C9 CYP3A4 P-gP	CYP2C19 CYP2C9 CYP3A4	CYP3A4 P-gP	CYP2C19 CYP2C9 CYP3A4	CYP2B6 CYP2C9 CYP3A4	CYP2C19 CYP2C9 CYP3A4	CYP2C19 CYP2C9 CYP3A4 P-gP	CYP3A4	CYP2C19 CYP2C9 CYP3A4 CYP2B6 CYP2E1 P-gP	CYP2D6 CYP2C9 CYP3A4	CYP2C19 CYP2CP CYP3A4 P-gP	CYP2C19 CYP2C9 CYP3A4	CYP2C19 CYP2C9 CYP3A4
ANTIBLASTIC DRUGS	Cyclophosphamide	CYP2B6 CYP2C9 CYP3A4 P-gP													
	Cysplatin	OCT2													
	Paclitaxel	CYP2C8 CYP3A4													
	Docetaxel	CYP3A4 P-gP													
	Irinotecan	CYP3A4 UGT1A1													
	Etoposide	CYP3A4													
	Doxorubicin	CYP3A4 P-gP													
	Tamoxifen	CYP2D6 CYP3A4													
	Letrozole	CYP2A6 CYP3A4													

No expected interactions; theoretical/potential interaction; low clinical relevance; possible or likely clinical relevance

Spp. Several species; CYP cytochrome P450 enzyme; P-gP P-glycoprotein; OCT2 Organic cation transporter-2; UGT1A1 UDP glucuronosyltransferase family 1 member A1.

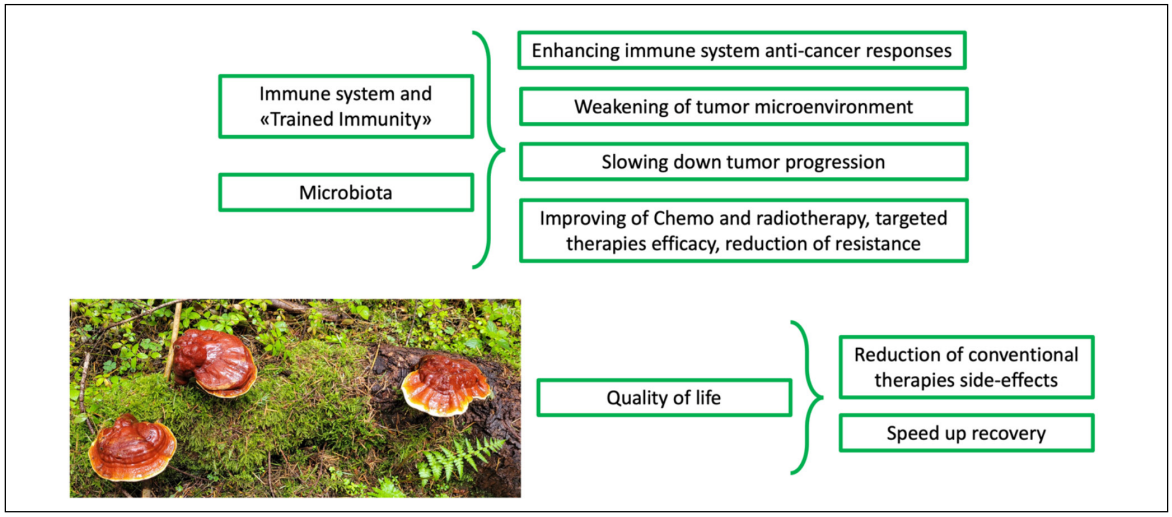

Figure 1. Positive effects of the supplementation of medicinal mushrooms in cancer patients

insomnia, and mucosal ulcers, and that it can improve and speed recovery. All of these effects can help improve patients' quality of life[25,30].

In conclusion, the use of mushroom supplementation in cancer patients may not only improve the quality of life, but also help reduce cancer progression by improving the immune response, weakening the tumor microenvironment, and strengthening the microbiota (Table III).

Table III. Main medicinal mushrooms used in oncology and their effects.

Main medicinal mushrooms used in oncology	Effects
Ganoderma lucidum - Reishi (whole mushroom + idroalcoholic extract)	Tumor microenvironment Microbiota Cardioprotection Neuroprotection (anxiety, mood, sleep quality) Immunosurveillance Reduces toxicity of CT Improves recovery Quality of life
Cordyceps sinensis (rich in cordycepin)	Tumor microenvironment Antiproliferative effect Pain reduction – anti-inflammatory effect Cardioprotection Radioprotection Reduces toxicity of CT Improves recovery Quality of life
Agaricus blazei Murrill (extract or whole mushroom)	Reduces toxicity of CT Immunosurveillance Improves recovery Quality of life
Grifola frondosa – Maitake (whole mushroom)	Reduces toxicity of CT Immunosurveillance Bone protection Improves recovery Quality of life
Auricularia auricula judae (whole mushroom)	Radioprotection Microbiota
Lentinus edodes – Shiitake (whole mushroom)	Microbiota Immunosurveillance Anti-cachexia

More studies are needed to collect data and optimize supplementation, but the existing data are definitely promising.

Immunonutrition as Integrative Approach in Cancer Patients

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The relationship between medicinal mushrooms, the microbiota, and the immune system is a topic of growing interest in the scientific community as the importance of the gut microbiota in regulating the immune system and overall health becomes more apparent. Medicinal mushrooms belong to a category of fungi that contain bioactive compounds with potential health benefits for humans.

Bioactive compounds found in medicinal mushrooms, such as beta-glucans, have the ability to modulate the immune response[31]. Beta-glucans activate immune cells, such as macrophages and lymphocytes, strengthening their capacity to identify and fight against pathogens[32,33]. Additionally, they improve tolerance to probiotic bacterial species, helping to maintain a healthy balance in the immune system[34].

Medicinal mushrooms are also a source of prebiotic fibers, which consist of polysaccharides that promote the growth of beneficial bacteria in the human intestine[35]. Some of these compounds exhibit antimicrobial properties against opportunistic pathogens and possess anti-inflammatory properties that create a favorable intestinal environment for the microbiota[34,36] (Figure 2).

Finally, medicinal mushrooms contain a range of compounds, including beta-glucans and other polysaccharides that are metabolized by the gut microbiota to form short-chain fatty acids (SCFA). Among these, butyrate plays an important role in human health, particularly in supporting gut health, regulating the immune system, and potentially influencing metabolic and mental health[37].

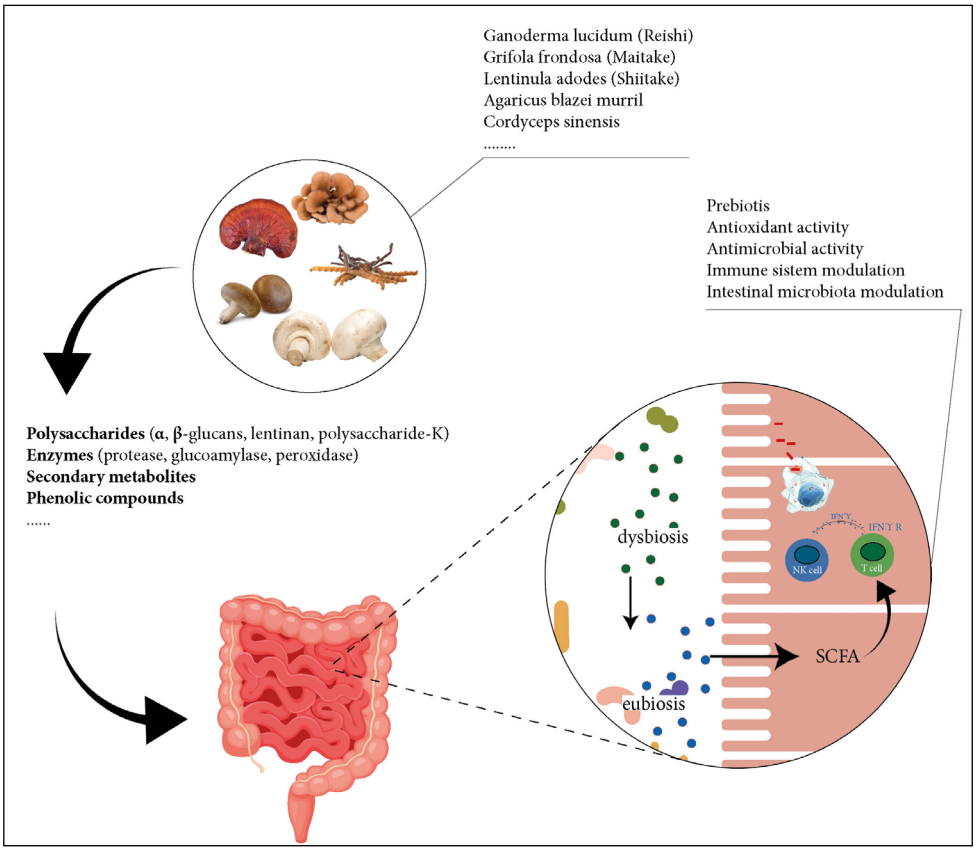

Figure 2. Medicinal mushrooms as allies for intestinal health. The main components of mushrooms have antioxidant, anti-inflammatory and antimicrobial effects in the intestine and modulate the microbiota and the immune system.

Sarcopenia in Cancer Patients: Integrated Therapeutic Strategies

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This session discusses the importance of physical activity and phytotherapy to contrast sarcopenia and osteopenia in oncology patients. Sarcopenia and osteopenia are two conditions that characterize the progression of cancer, both as a direct effect of the disease on the organism and as a typical phenomenon of aging. About 60% of cancer cases occur at age 65 and older. An age in which the fragility of the organism increases and which, in cancer patients, is also exacerbated by the toxicity of the therapies to which they are subjected to fight the disease itself. Sarcopenia, or the progressive and general loss of mass, skeletal muscle strength, and physical performance, negatively affects the overall health of the individual. Sarcopenia has also been associated with low bone mineral density (BMD), a condition known as osteopenia. This suggests that low muscle mass reduces the mechanical load on the skeleton, resulting in reduced bone formation. The two conditions often occur together and are defined by a single term: osteosarcopenia.

Today, osteosarcopenia has been shown to be a predictive factor for the prognosis of patients undergoing liver resection for colorectal liver metastases (CRLM)[38]. From the study of Furukawa et al[38] emerged that in univariate and multivariate analysis, osteosarcopenia was a strong predictor of adverse outcomes in patients undergoing liver resection for CRLM. Patients with osteosarcopenia had more women than men and lower body mass index (BMI) compared with patients without osteosarcopenia.

Osteosarcopenia and inflammation

Osteosarcopenia is treated nutritionally with protein supplementation and/or vitamin D and calcium, which are certainly necessary supplements in the case of an identified deficiency. Today, however, another determining factor in the causality of these two diseases is inflammation[39]. Very often, osteosarcopenia, typical of the elderly, is accompanied by an increase in chronic low-grade inflammation, the causes of which are often related to lifestyle, poor diet, lack of exercise, chronic stress, obesity, etc.

Physical activity is a valid and effective method to prevent and improve the conditions of osteosarcopenia. Depending on the age and clinical condition of the subject, important strategies of combined work can be applied: aerobic, anaerobic, and stretching training with the aim of maintaining and improving both muscle mass and bone remineralization through mechanical stimuli and the anti-inflammatory effect of exercise[40].

Another important garrison to treat the inflammatory aspect is undoubtedly phytotherapy.

Plants with anti-inflammatory action, such as *Curcuma Longa*, when used in phytosomal form, do not lead to pharmacokinetic activation of metabolism and are therefore compatible with the therapies adopted by the cancer patient[41]. In addition, *Curcuma Longa* helps to sensitize cancer cells to chemotherapy and protect normal cells from further chemotherapy-induced damage than to protect against the toxic effects of chemotherapeutic agents by attenuating their collateral effects[42].

Vitamine D3: Role in the Modulation of the Immune System and Bone Health

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Vitamin D enters the body about 20% from food or 80% is synthesized by the skin from 7-dehydrocholesterol, the last precursor of cholesterol in its biosynthetic pathway, after UVB exposure. The liver enzyme CYP2R1 converts vitamin D3 to 25-hydroxyvitamin D3 (25(OH)D3). Serum levels of 25(OH)D3 are used as a biomarker of vitamin D status because it is the most abundant and stable vitamin D metabolite with a half-life of approximately 3 weeks. In the kidneys, 25(OH)D3 is further hydroxylated by the enzyme CYP27B1 to 1α,25-dihydroxyvitamin D3, which binds with remarkably high affinity to the nuclear receptor vitamin D receptor (VDR). Vitamin D status is largely dependent on an individual's lifestyle and genetic variations[43].

It plays a main role in the calcium homeostasis and bone metabolism. Vitamin D is involved in directing the osteoblasts towards proliferation or apoptosis, regulates their differentiation to bone matrix-producing cells, and controls the subsequent mineralization of the bone matrix (Figure 3).

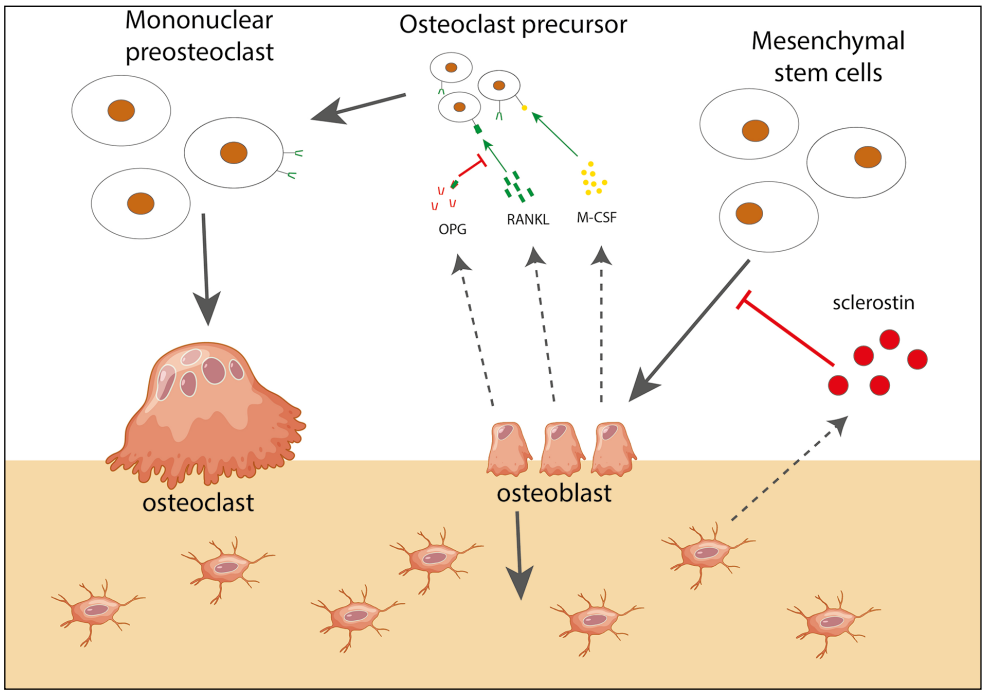

Figure 3. Bone remodeling and metabolism: role of osteoblasts and osteoclasts[44].

In addition, vitamin D exhibits other important effects known as "non-classical effects". It regulates the function of immune cells and the differentiation and proliferation of hematopoietic cells. The fact that more than half of human tissues express the *VDR* gene indicates that 1,25(OH)2D3 and its receptor have a pleiotropic function in pathways of energy metabolism, immunity, and cell growth and differentiation[45,46].

Regulation of CYP27B1 synthesis in immune cells is distinct from signals regulating renal production of 1,25(OH)2D3. Inflammatory signals, such as lipopolysaccharides (LPS) and cytokines, induce CYP27B1 production in monocytes and macrophages. These differences in the regulation of 1,25(OH)2D3 production suggest an autocrine/paracrine effect as immunomodulatory. *Via* VDR, vitamin D modulates the activity of both the innate and adaptive immune systems. In monocytes, for example, vitamin D stimulates efficient recognition of bacterial pathogens *via* Toll-like receptors, and in macrophages, it inhibits the proliferation of *M. tuberculosis*. Vitamin D has also been shown to prevent other types of microbial infections, such as respiratory and urinary tract infections. In addition, 1,25(OH)2D3 increases the production of the antimicrobial peptides defensin 2 and cathelicidin by macrophages and monocyte keratinocytes, thereby increasing their antimicrobial activity. In addition, 1,25(OH)2D3 increases chemotaxis, autophagy, and phagolysosomal fusion of cells of the innate immune system.

In addition, vitamin D inhibits differentiation, maturation, and the immunostimulatory capacity of dendritic cells. The resulting immune tolerance-inducing phenotype of dendritic cells leads to the induction of regulatory T cells down-regulating the activity of other cells of the immune system. This is the central mechanism of how vitamin D dampens chronic inflammation and autoimmunity in diseases such as inflammatory bowel disease and multiple sclerosis.

Moreover, vitamin D is able to reinforce the physical barrier function of epithelial cells. In particular, 1,25(OH)2D3 can improve the barrier function of the cornea and intestinal epithelium. Literature suggest that vitamin D is one of the players in the complex relationship between gut microbiota (GM) and immune system modulation.

The 25(OH)D3 modulates the adaptive immunity. Early studies have shown that the VDR is highly expressed post- activation in both B and T lymphocytes. By binding to the VDR on T cells, vitamin D modulates the differentiation and activation of CD4+ lymphocytes. Tregs, a subset of CD4+ lymphocytes, suppress the immune response and mediate immune tolerance.

In addition, vitamin D signaling enhances the numbers of Tregs both in patients with inflammatory diseases and healthy controls. Interestingly, vitamin D suppresses T lymphocytes proliferation by reducing *IL-2* gene transcription, and inhibiting the production of pro-inflammatory Th-cytokines, including, IFN-γ, IL-2, and IL-17. It has been suggested that 1,25(OH)2D3 acts as an immunomodulatory not only by suppressing Th1 cells activation, but also modulating Th2 cells, T regulatory cells activity, and Th17 cells. It also appears that vitamin D suppresses proliferation, production of immunoglobulins in B cells, and differentiation of B cells into plasma cells. In addition, vitamin D inhibits the formation of memory B cells and the secretion of immunoglobulins IgG and IgM in activated B cells.

Although there are preclinical and observational data suggesting that maintaining adequate vitamin D levels should help prevent the occurrence of autoimmunity, current evidence on the therapeutic benefits of supplementation is inconclusive, and many studies are limited because of small group sizes. Further studies are needed to better elucidate the role of vitamin D as an immunomodulator in humans and to reach a consensus on the most appropriate vitamin D3 supplementation. Vitamin D has anticancer effects both directly by controlling differentiation, proliferation, and apoptosis of neoplastic cells and indirectly by regulating immune cells that are part of the microenvironment of malignant tumors[47,48].

Preliminary Results by an Integrative and Multidisciplinary Oncological Approach

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OBJECTIVE: The critical role of Integrative Medicine (IM) in reducing the Adverse Events (AEs) of anti-cancer treatments (ACTs) and improving Quality of Life (QoL) in cancer patients has already been demonstrated1-3. According to the National Cancer Institute (NCI), the IM approach to medical care combines traditional medicine (TM) with complementary medicine (CM) practices proven safe and effective1-3. We present our preliminary results on the use of an IM approach in cancer patients.

PATIENTS AND METHODS: We retrospectively collected data on 38 cancer patients treated with supportive care (SC) using an IM approach, which was adopted when TMs failed or, in most cases, in addition to ACTs, with the aim of improving QoL and reducing AEs associated to ACTs. The IM mainly consisted of vitamin C-D, probiotics, NAC, diet, and a blend of medicinal mushrooms (Reishi, Maitake, Agaricus-blazei, Cordyceps-sinensis, and Shitake) in most patients and was combined with TM and ACTs in some cases. Oncologists filled the prescription of IM in most cases. The type of IM approach was decided according to the clinical conditions of the patients and the kind of symptoms.

RESULTS: Table IV reports patients' characteristics. Overall, the IM approach was well tolerated, and no serious side effects occurred. No significant interactions between IM and ACTs were observed, and the risk of drug-herb interactions was assessed in 10 patients. In addition, IM proved to enhance QoL in most treated patients; 4 patients showed significant prolongation of overall survival, and 2 patients with metastatic breast cancer showed complete hematologic recovery (Table IV).

CONCLUSIONS: Our IM approach is a typical combination of TM and CM, which has been shown to be safe and effective. The efficacy of IM in controlling cancer in

Table IV. Clinical Patients characteristics treated with IM.

Number of patients	38 (%)
Sex	
Male	14 (37)
Female	24 (63)
***Age**	63 (36-83)
***Performance Status ECOG**	
0-1	26 (68)
2-3	12 (32)
Type of cancer	
Breast	10 (26)
°CNS	8 (21)
Colon	6 (16)
Others	14 (37)
Stage of disease	
Early	4 (10)
Advanced	19 (50)
Metastatic	
15 (40)	
Concomitant use of IM+TM	
Yes	30 (79)
No	8 (21)
Toxicity by IM	
Yes	1 (3)
No	37 (97)
Interactions test IM+TM	
Yes	10 (26)
No	28 (74)
Results by IM	
Toxicity reduction	6 (16)
↓ CRF	16 (42)
↑ QoL	18 (32)
Disease Response	4 (10)
^Median duration of IM	5 (1-17)

*Median; °Central Nervous System; ^Months; IM: Integrative medicine; TM: Traditional medicine; CRF: cancer-related fatigue; QoL: Quality of life.

4 patients, the improved QoL, and the good tolerability of ST demonstrated in all cases speak to the value of this approach in patients with acceptable performance status whose cancer is refractory to standard ACTs or who are affected by persistent AEs. It should be noted that many of the products used in ST may affect microbiome activity. Clearly, our data need to be confirmed in well-designed prospective clinical trials. In summary, our retrospective analysis confirms that IM can improve the QoL and reduce the AEs associated with ACTs without toxicity or risk of interactions.

Adapted Physical Activity as Rehabilitation Program in Breast Cancer Patients: focus on "Fenice" and "Nastro Rosa" Clinical Trials

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INTRODUCTION: Breast cancer (BC) represents one of the more frequent cancer diseases in Western Countries[49-51]. In recent decades, conservative surgery has become the first choice whenever possible, making mastectomy the preferred option only in selected cases. However, surgery is still associated with numerous adverse effects, including pain, edema, and limited mobility[52]. Posture often appears to be altered after mastectomy because arm mobility is affected by the surgical scars (for example, internal rotation and shoulder drop are common, typically causing back pain). Moreover, the removal of lymph nodes in both sentinel surgery and axillary lymph node dissection is reported as a common reason for limited mobility and postoperative pain. In addition to surgical procedures, oncologic medical treatments are also associated with numerous long-term side effects, including increased pain, fatigue, lymphedema (after adjuvant RT treatment), peripheral neuropathy, neurocognitive dysfunction, and increased risk of developing cardiovascular disease, respiratory impairment, metabolic dysfunction, sexual dysfunction, impaired mental health (e.g., depression and anxiety)[53-56]. Finally, the use of endocrine therapy with aromatase inhibitors has been associated with a possible risk of arthralgias and deterioration of bone health. All these aspects negatively affect the health-related QoL of BC survivors. Some randomized clinical trials have shown the benefits of reconditioning by regular and appropriate Adapted Physical Activity (APA) during and after BC treatment, especially in terms of health benefits, fatigue reduction, strength level improvement, QoL, and physical function[56,57]. In this context, the APA as fencing has demonstrated its affinity and effectiveness as a treatment support during and after treatments for BC patients.

OBJECTIVE: The aim is to determine whether the practice of APA as fencing in non-metastatic BC patients results in 1) an overall reduction in side effects (Table IV) associated with oncologic treatments (surgery, radiotherapy, and drugs); 2) an overall improvement in cancer-related fatigue (CRF), HR-QoL, anxiety, depression, vitality, sleep quality, BMI, aspects of bone health, lower and upper extremity strength, flexion and external rotation of the operated arm, aerobic capacity, heart rate, and overall health status.

PATIENTS AND METHODS: A prospective, randomized, single-center clinical trial has been conducted at Policlinico Tor Vergata and ASD Frascati Scherma (Figure 4). Patients of any ethnicity who are at least 18 years of age and have been diagnosed with non-metastatic BC over the last six months have been involved in the study. Patients in the study arm have received BC therapies along with APA fencing, whereas patients in the control arm will receive the standard of care without APA. All patients undergo clinical examinations (surgical, oncological, nutritional, cardiological, physiatrist, psychological), laboratory, and instrumental examinations (according to the physicians' suggestions) and are then randomly assigned to an APA program or to the control group. For the study arm, the APA intervention is carried out at ASD Frascati Scherma by selected fencing instructors with the collaboration of doctors in Motor Sciences, and it will last for a minimum of 6 months. Physicians and psychologists can use clinical, laboratory, and instrumental results to guide fencing coaches' adapted training via the intensity and duration of an APA intervention. Patients in the control group are provided with the standard of care without APA. Results of the preliminary examinations are recorded in the (electronic) medical record and provided to the patient in the form of a clinical report.

ENDPOINTS: The primary objective of the FENICE clinical trial is an improvement in the overall physical and mental status of patients in the study group compared with patients in the control group. Secondary endpoints include improvement in clinical parameters measured by instruments and laboratory tests (e.g., serum lipids, glycaemic profile, bone density measurement, fatty liver, immune profile, etc.) for patients in the study group.

If patients choose to participate in the FENICE clinical trial, they may be randomized to the intervention arm. In this case, the burdens on the patient are: (1) regular participation in APA (fencing adapted to disability); (2) regular contact by a research nurse, and completion of a questionnaire.

Conclusions

The IM plays a key role in the treatment of cancer patients, and this type of approach should be shared by physicians and patients[58-60] (Table V).

Unfortunately, most physicians' lack of knowledge about CIM and their limited communication with patients have negative consequences on clinical management and outcomes[3]. In addition, it has been demonstrated[4] that the use of alternative

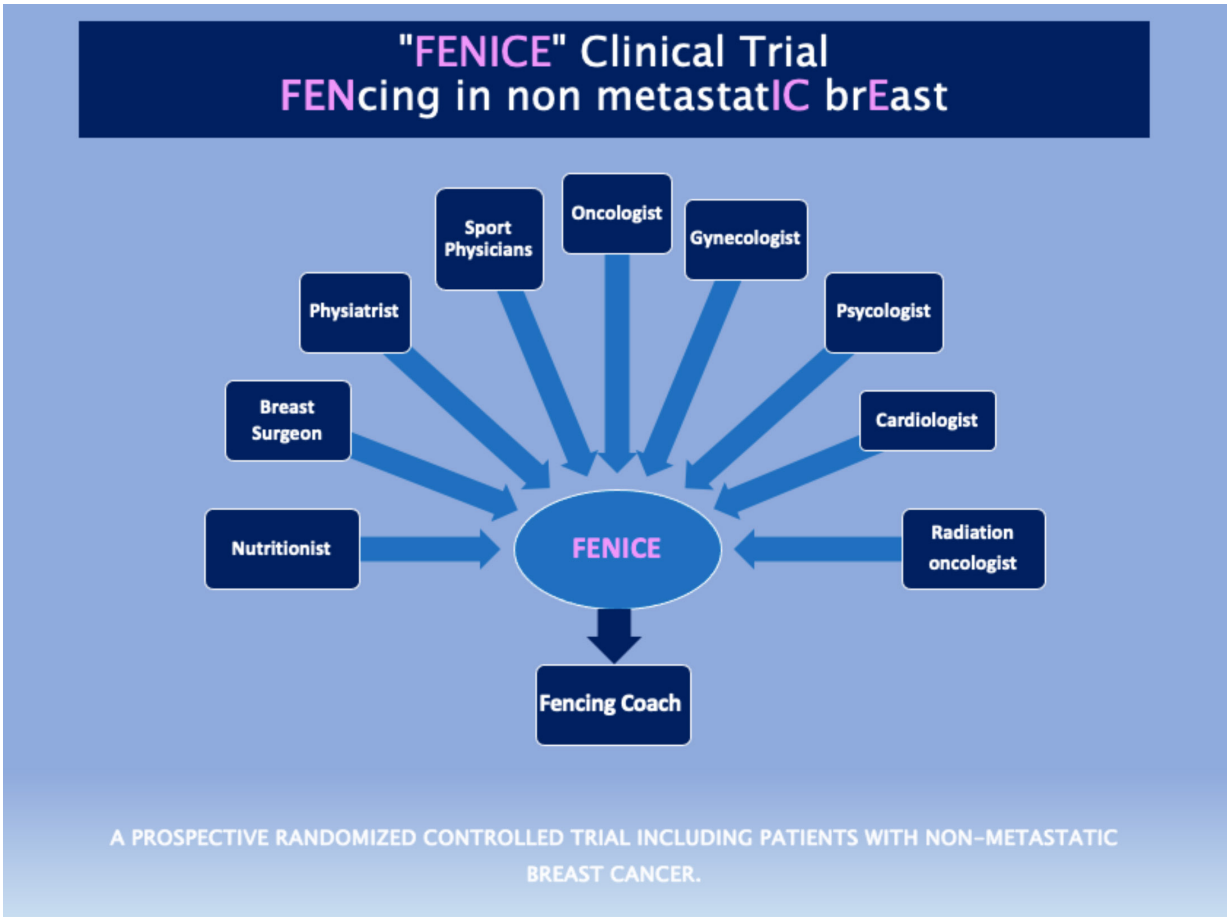

Figure 4. Research team of FENICE clinical trial.

medicine instead of CM within a CIM approach is associated with worse five-year survival in a cancer setting[61]. Considering that about 60% of cancer patients use CAM without medical indication, the risk of drug-natural product interactions is high[2,11].

In addition, the use of CAM is also common in patients with chronic diseases or chronic symptoms[2,58], as reported in the literature. In view of the above, we are confident that the CIM approach within a multidisciplinary team is a good way to provide the best integrative approach to improve HR-QoL in cancer patients, chronically ill patients, and so-called frail patients[62-76].

To date, monitoring of the risk of drug and/or herbal remedy interactions in clinical practice is still very limited, although interaction checker programs exist (e.g., Lexicomp[77], Medscape[78], and Micromedex[79]). The databases of these programs include drugs and several commonly used herbs and allow qualitative and quantitative analysis of the risk of interactions based on scientific data.

However, there is still a need to update and enrich the databases of these programs with herbal remedies, which are increasingly used by patients as co-medications. For cancer patients in particular, risk assessment of drug/herb interactions becomes imperative, given the use of drug combinations in cancer therapies and the fact that patients are increasingly already taking drug therapies at the time of diagnosis. Pharmacologic counseling of cancer patients requires interdisciplinarity, but especially knowledge of the widely used dietary supplements and herbal remedies.

The scientific activity of IMRG is focused on the organization of prospective studies with the aim of improving knowledge about different categories of patients treated within a multidisciplinary and integrative approach. Scientific and practical information about integrative medicine in cancer patients is described in Table V.

Table V. Reputable resources for information about Integrative Medicine and Complementary Therapies in cancer settings.

American Cancer Society: Guidelines for Using Complementary and Alternative Methods (available at: http://www.cancer.org/Treatment/TreatmentsandSideEffects/ComplementaryandAlternative).
Integrative Medicine Research Group (IMRG) - (available at: http://www.imrg.it)
Medline Plus (available at: http://www.nlm.nih.gov/medlineplus/druginfo/herb_All.html).
Memorial Sloan-Kettering Cancer Center (MSKCC) About Herbs, Botanicals and Other Products (available at: http://www.mskcc.org/aboutherbs and www.MSKCC.org/IntegrativeMedicine).
National Cancer Institute: Topics in Complementary and Alternative Therapies (PDQ) (available at: http://www.cancer.gov/cancertopics/ pdq/cam/topics-in-cam/health professional).
National Center for Complementary and Alternative Medicine (NCCAM) (available at: http://nccam.nih.gov/health/cancer/camcancer.htm).
NCCAM Time to Talk Toolkit: Ask Your Patients About Their Use of Complementary Health Practices (available at: http://nccam.nih.gov/ time to talk/forphysicians.htm).
NIH Office of Dietary Supplements (available at: http://ods.od.nih.gov/).
Society for Integrative Oncology (available at: http://www.integrativeonc.org/).
United States Pharmacopeia (USP) Dietary Supplement Standards (available at: http://www.usp.org/dietary-supplements/overview).
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Conflict of Interest

Dr. Pier Paolo Zanello, Dr. Daniele Santagà, and Dr. Stefania Cazzavillan are scientific consultants for AVD Reform.

Acknowledgements

The authors of the abstracts thank AVD Reform (Noceto, Parma, Italy) for the organization of the conference and contribution to editing the English text and IMRG for scientific support.

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