

The role of integrative and complementary medicine in the management of breast cancer patients on behalf of the Integrative Medicine Research Group (IMRG)

M. BERRETTA¹, F. FRANCESCHI², V. QUAGLIARIELLO³, M. MONTOPOLI⁴,
S. CAZZAVILLAN⁵, P. ROSSI⁵, P.P. ZANELLO⁶

¹Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

²Department of Emergency Medicine, Polyclinic "Agostino Gemelli" University Hospital, IRCCS, Rome, Italy

³Division of Cardiology, Istituto Nazionale Tumori IRCCS-Fondazione G. Pascale, Naples, Italy

⁴Department of Pharmaceutical Sciences, University of Padua, Padua, Italy

⁵Department of Biology and Biotechnology "L. Spallanzani", University of Pavia, Pavia, Italy

⁶AVD Reform Scientific Direction, Noceto (PR), Italy

Abstract. – The aim of this conference was to explain the role of integrative and complementary medicine in breast cancer patients. The topics covered are numerous and their peculiarities are the multidisciplinary characteristics of the researchers involved. The Integrative Medicine Research Group (IMRG) believes in the complementary and integrative approach in cancer patients to improve the quality of life in this particular setting.

Key Words:

Breast cancer, Patients, Microbiota, Treatment, Nutrition, Integrative medicine.

Introduction

The Integrative Medicine Research Group (IMRG) presents here a new conference scene on the role of complementary and integrative medicine in the management of breast cancer (BC) patient.

Breast cancer is the most frequent cancer among women worldwide, impacting 2.1 million women each year. While BC is less common at a young age, younger women tend to have more aggressive BCs than older women. In 2018, it is estimated that 627,000 women died from BC; that is approximately 15% of all cancer deaths among women. The main associated risk factors include family history, menstrual and reproductive history (nulliparity, late age at first birth, early

menarche, and late menopause), as well as high alcohol consumption, being overweight, obesity, and lack of physical activity¹. High-penetrance gene mutations (BRCA1, BRCA2, TP53, PTEN) considerably increase BC risk, however, they only account for a small proportion of the disease burden given their low frequency in the population^{1,2}. To date BC patients, have available a lot of treatment options as surgery, antineoplastic chemotherapy (AC), target therapies (TT), hormonal therapy and radiation. While these treatments are able to improve the survival in these patients at the same time their quality of life (QoL) is often compromised with all the above-mentioned treatment strategies. It is not surprising to see a huge number of BC patients seeking help through nutraceuticals as a complementary and/or as alternative therapy. This kind of approach is known under the term of Complementary and Alternative Medicine (CAM)³.

According to the National Center Institute of USA for Complementary and Integrative Health (NCCIH), CAM therapies include a wide spectrum of practices and products, either biological (e.g., herbs or botanicals, vitamins, minerals, probiotics, homeopathic products, and Chinese herbal remedies) or non-biological (e.g., prayer, meditation, music therapy, yoga). These interventions are defined as "alternative" when they are used instead of Conventional Medicine (CM) and as "complementary" when they are used in combination³⁻⁶.

The aim of this conference scene, organized by IMRG in Italy, is to focus on the role of Integrative treatment in the management of BC patients in the context of a multidisciplinary and innovative approach, including CAM that has been shown to be safe and effective.

Oral Session

Role of the GUT Microbiota in Breast Cancer: State of the Art and Clinical Evidences

Prof. Francesco Franceschi, MD
Department of Emergency Medicine, Polyclinic Agostino Gemelli University Hospital, IRCCS 00168 Rome, Italy

The role of the GUT microbiota in health and disease represents one of the most emerging topics among modern medicine. In the last years, many studies⁷⁻¹¹ have been performed concerning its role in carcinogenesis, not only confined to the GI tract but also in other districts, including the breast. Breast tissue, in fact, exerts its own microbiota, which differs from that observed in the GUT. While GUT microbiota is characterized by a great number of species, breast microbiota shows a lower number of bacteria, with an increased concentration of *Prevotella*, *Lactococcus*, *Streptococcus*, *Corynebacterium* and *Micrococcus* and a reduced expression of *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Bacteroidetes*. Moreover, inside breast cancer tissue there is an abundance of *Enterobacteriaceae*, *Staphylococcus*, *Corynebacterium*, *Actinomyces* and *Propionibacteriaceae*. Recent studies⁷⁻¹¹ also reported an increased concentration of *Methylobacterium radiotolerans* inside estrogen-positive breast cancer tissues, while it was reduced in invasive forms. Another interesting data¹¹ is the reduction of Lactobacilli in breast cancer tissue and this clearly demonstrates that breast cancer is associated with a local dysbiotic process. This phenomenon, together with all other known risk factors, including age, family history, smoking, obesity, gestation or lactation, may enhance the risk of acquiring breast cancer. Finally, there is also evidence of a crosstalk among GUT and breast microbiota, which is also due to the ability of microbes to produce some active substances, such as estrogens, phytoestrogens, short chain fatty acids, lithocholic acid and cadaverine, all able to influence the occurrence and growth of

breast cancer. In this way, GUT microbiota by altering the concentration of estrogens, may affect the transition from dysplasia to neoplasia or the response to antineoplastic drugs. On this subject, there are some ongoing trials designed to verify the possible protective effects of probiotics in GUT or breast carcinogenesis, but data produced are too scarce. Further studies are needed to verify their real effectiveness, especially in association to Mediterranean diet, which seems to show a protective effect⁷⁻¹¹.

The Importance of a Proper Lifestyle and Nutrition in Patients with Breast Cancer

Vincenzo Quagliariello, Ph.D
Division of Cardiology, Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale of Naples, Naples, Italy

A global increase in BC incidence has been seen in the last years. The rates of estrogen receptor (ER)-positive breast cancer incidence are increasing, therefore, some environmental and life-style factors are involved in BC pathogenesis¹². A recent meta-analysis¹³ clearly show that obese subjects have a higher incidence of both premenopausal and postmenopausal BC; furthermore, women with metabolic syndrome have a higher risk of both incidence and recurrence of BC. As the number of metabolic syndrome factors increases (up to 5 factors), especially if testosterone levels are also high, the relative risk of incidence and recurrence is higher than in non-obese/no metabolic syndrome women¹⁴.

From a molecular point of view, it is clear that high cholesterol, especially oxysterols, arachidonic acid products (i.e., leukotrienes), advanced glycosylation products (AGEs), hyperglycemia and fructosylation are pro-oncogenic factors that stimulate cancer cell survival pathways especially through the pAMPK/ Tuberous sclerosis complex inhibition and consequent induction of mTOR, NLRP3 inflammasome and associated pro-inflammatory cytokines¹⁵.

Conversely, calorie restriction, physical activity, antidiabetic drugs, including SGLT2 inhibitors, metformin and nutraceuticals, counter these pro-oncogenic pathways. Free fatty acids and mediators of the cholesterol synthesis play a key role in BC initiation (through the reduction of DNA repair mechanisms) and progression (through the over stimulation of the estrogen and leptin receptors and the reduction of adiponectin levels)¹⁶.

Patients unresponsive to aromatase inhibitors have a greater expression of key enzymes in the biosynthesis of endogenous cholesterol, therefore, they follow a nutrition aimed at lowering cholesterol levels could be of key importance to improve the efficacy of aromatase inhibitors in neo-adjuvant BC patients¹⁷.

Free fatty acids are associated to insulin resistance, non-alcoholic fatty liver disease, visceral obesity and inflamed breast fat¹⁸. Recent research¹⁹ has shown that peri-mammary adipocytes grow under high glucose increase cell survival and metastasis signals in BC cells through paracrine mechanisms. Furthermore, hyperglycemia reduces the efficacy of immuno-checkpoint inhibitors, possibly by increasing IL-6 and IL-1 levels which are associated with a lower recognition of CD-8 and CD-4 T-lymphocytes against cancer cells. Recently, new antidiabetic drugs called gliflozines (selective SGLT2 inhibitors) have shown protective cardio-renal activities in particularly vulnerable patients and preclinical association studies with aromatase inhibitors are currently ongoing^{20,21}.

Breast cancer patients should follow the European Cancer Code recommendations; briefly, the European Code Against Cancer suggests daily consumption of low-calorie foods with a wide variety of vegetables and whole grains²². It is therefore necessary to choose foods with a low glycemic and insulinemic index, and with a low glycemic load in order to reduce the pathways related to free fatty acids, chemokines and endogenous cholesterol.

The Role of Integrative and Complementary Medicine in the Management of Breast Cancer Patient

Prof Massimiliano Berretta, MD, Ph.D
Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

According to National Cancer Institute (NCI) guidelines the Integrative Medicine is an approach to medical care that combines conventional medicine (CM) with CAM practices that have shown, through science, to be safe and effective²³. This approach often stresses the patient's preferences, and it attempts to address the mental, physical, and spiritual aspects of health. We know that about of 80% of patients with BC reported using CAM therapies in their treatment regimens to enhance immune function, reduce cancer symptoms, prevent cancer relapse, and

control emotional anxiety²⁴. Moreover, BC survivors were 36% more likely than the general population to have used CAM therapies, typically for the purpose of alleviating post-conventional treatment symptoms²⁵.

We can distinguish five categories of CAM and as following reported:

Mind-Body Therapies, that combine mental focus, breathing, and body movements to help relax the body and mind. Some examples are: meditation, bio-feedback, hypnosis, yoga, tai chi, imagery and creative outlets.

Biologically Based Practices, that uses things found in nature. Some examples are: vitamins and dietary supplements, botanicals (plants or parts of plants, as cannabis, aloe, mushrooms), herbs and spices and special foods or diets.

Manipulative and Body-Based Practices, that are based on working with one or more parts of the body. Some examples are: massage, chiropractic therapy (a type of manipulation of the spine, joints, and skeletal system) and reflexology (using pressure points in the hands or feet to affect other parts of the body).

Biofield Therapy, also called energy medicine, involves the belief that the body has energy fields that can be used for healing and wellness. Some examples are: reiki and therapeutic touch.

Whole Medical Systems, that are healing systems and beliefs that have evolved over time in different cultures and parts of the world. Some examples are: Ayurvedic medicine (from India and based on the restore balance between body, mind and spirit), traditional Chinese medicine (acupuncture, the right balance in the body of two forces called yin and yang), homeopathy and naturopathic medicine.

Some CAM therapies have undergone careful evaluation and have been found to be generally safe and effective. These include acupuncture, yoga, meditation, some vitamins, dietary supplements, botanicals to give some examples. However, there are others that do not work, may be harmful (Laetrile), or could interact (St. John's wort) negatively with oncological treatments²³. Despite claims of promising and potential benefits made by CAM treatment prescribers, many CAMs lack good scientific evidence of their safety and effectiveness. For the most of CAM, and according to English literature, their role is that of support treatment, able to improve the QoL during and after oncological treatments. One of the most famous and commonly consumed supplements, in cancer

patients, is Vitamin C^{26,27} that has demonstrated to improve BC survival in one meta-analysis of 5 patient cohort studies and to have a good safety profile with concomitant administration of AC²⁸. Other CAMs, of particular interest for their multi action properties in cancer setting, are medicinal mushrooms (Med Mush). In fact, in the last decade the activities of Med Mush, particularly for *Trametes Versicolor* and *Ganoderma lucidum* have demonstrated to improve disease free survival (DFS) or progression free survival (PFS) and overall survival (OS) in patients affected by Gastric, Colorectal and Lung cancer, while in BC a phase I clinical trial has demonstrated a statistically significant increase in CD8+ cytotoxic T cells ($p = .0003$), CD19+ B cells ($p = .0334$) and NK cells ($p = .043$) in a dose-dependent manner²⁹. The main activity, demonstrated by Medicinal Mushrooms, is the immunomodulation and potentiation of immune surveillance³⁰. An aspect that requires more attention is the poor communication between physicians and patients on CAM use. In fact, while the safety and advantages of CAM are causing its growth in popularity, 70% of patients reported their physicians did not take time to discuss it with them as an option and only 16% of patients believed the physician was well informed about CAM treatment. Therefore, it is imperative that further research will be conducted to elaborate on CAM's effects on the OS and recurrence rates in BC patients.

Pharmacological Aspects and Clinical Evidence of Anticancer Treatments in Synergy with Phytotherapy Drugs

Prof. Monica Montopoli, Ph.D

Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Padua, Italy

Nowadays BC is the most diagnosed tumor among women worldwide and remains one of the leading causes of cancer death. Breast cancer is a heterogenous disease classified in different subtypes, depending on molecular or histopathological aspects, such as different expressions of hormonal receptors or growth factors. The triple-negative subtype (estrogen receptor-negative/progesterone receptor-negative/human epidermal growth factor receptor (HER2)-negative) and the hormone-independent (HER2+ or HER2-) tumors represent the most aggressive subtypes, with poor prognosis, high metastatic potential, and drug resistance³¹. In particular, triple-neg-

ative BC (TNBC) subtype lacks receptors for targeted therapy, thus chemotherapy still remains the standard treatment. Despite the potential effect of chemotherapy, the severe toxicity caused by these approaches limits its clinical use patient wellbeing.

In the last decades, researchers suggested that the addition of natural compounds to standard therapy could allow lower drugs dosage, thus reducing adverse effects. Literature studies³²⁻³⁸ reported the antitumor effect of natural molecules, such as resveratrol, sulforaphane genistein, lycopene, and curcumin, and that the combined therapy is a promising strategy to overcome the drug resistance"DOI": "10.26355/eurrev_2021_110_26986", "ISSN": "1128-3602, 2284-0729", "issue": "20", "language": "eng", "page": "6174-6175", "source": "DOI.org (CSL JSON.

Several preclinical and clinical studies^{32,35,39,40} showed the chemo-preventive and antitumor effect of curcumin in cancer therapy, and the beneficial properties obtained with its combination and standard chemotherapeutic agents, such as cisplatin, doxorubicin and paclitaxel. In particular, the combination therapy improved the efficacy of chemotherapy, thus resulting in a promising tool to overcome drug resistance, as well as decreased side effects of standard care, such as dermatitis induced by radiation or fatigue in cancer patients^{41,42}hormone-independent HER2 negative breast cancer, also known as triple negative breast cancer (TNBC).

Recently, clinical studies^{43,44} demonstrated the beneficial effect of *Boswellia serrata* in reducing adverse effects, such as skin irritation, caused by radiotherapy in BC patients. In particular, *Boswellia serrata* showed anti-inflammatory and anti-phlogistic properties. It has been demonstrated⁴⁵ that the topical application of a cream with *Boswellia* during radiotherapy slightly reduced the side effects, such as burning sensation and itching.

In conclusion, the combination of phytotherapy with chemotherapy is beneficial for the chemo-preventive and antitumor effects, as well as for the reduction of side effects when administered as adjuvant therapy.

Medicinal Mushrooms as an Integrative Adjuvant Therapy in Breast Cancer

Prof. Stefania Cazzavillan, B.Sc. Genetics, Nutritionist

Contract Professor at the University of Pavia and University of Milan, IMRG Scientific Committee

Medicinal mushrooms manifest an impressive array of health-promoting activities including anticancer, immunomodulating, antihyperglycemic, antihypertensive, neuroprotective, hepatoprotective, antimicrobial, prebiotic, and antiviral activities.

Different mushroom bioactive compounds isolated from fruiting bodies and mycelium have demonstrated antitumor activity in *in vitro* and in preclinical animal models even with particular reference to BC which affects innumerable women worldwide, and in 2018, has been the leading cause of cancer death in females⁴⁶.

Inclusion of mushrooms in the diet is also protective against cancer⁴⁷. Many Med Mush compounds prevent oncogenesis, show direct *in vitro* antitumor activity, and prevent tumor metastasis.

Medicinal mushrooms are also considered “novel prebiotics”. An increasing number of scientific papers highlights that mushroom health-promoting properties are also related to their regulating effect on microbiota, which has a key role in cancer prevention, progression and treatment.

Their activity is especially beneficial when used in conjunction with chemotherapy since they reduce multidrug resistance and drugs’ side effects as well as rejuvenating the immune system weakened by radiotherapy and chemotherapy in cancer treatment⁴⁸.

Breast cancer is the most common invasive form of female cancer in the last few decades, and advanced breast cancers is a major concern since they do not respond well to therapy.

Studies⁴³⁻⁴⁸ on Med Mush and their biological compounds, such as beta-glucans, polysaccharide/protein complexes and secondary metabolites, demonstrate the potential activity of Med Mush in BC treatment.

Beta-glucans are safe to use, non-immunogenic and well tolerated. A main feature of β -glucans is their capacity to function as biological response modifiers, exerting regulatory effects on inflammation and shaping the effector functions of different innate and adaptive immunity cell populations. They reduce the inflammation and the toxicity of the tumor microenvironment thus reducing the progression of cancer. Beta-glucans, taken orally as food supplements, also exert a synergistic effect with conventional chemotherapy, monoclonal antibodies⁴⁹ and with immunotherapy⁵⁰.

Medicinal Mushroom (whole mushroom and extracts), such as *Ganoderma lucidum* and *Cordy-*

ceps sinensis are among the most studied in BC.

Ganoderma lucidum has shown the most significant inhibitory effect on NF- κ B activity in highly invasive BC cells and has synergistic activity with chemotherapeutic drugs such as tyrosin kinase inhibitors⁵¹. It reduces side effects (cardiotoxicity, nephrotoxicity, bone marrow toxicity etc.) and cancer related fatigue during chemotherapy and hormone deprivation therapy, improving the quality of life of the patients.

Cordyceps sinensis and its powerful metabolite cordycepin (the adenosine analogue 3'-deoxyadenosine) are emerging candidates in adjuvant cancer therapies.

Cordyceps sinensis has been a subject of research for approximately 50 years, which demonstrate its numerous cancer protecting activities, such as inhibiting tumor growth, inducing apoptosis, reducing inflammation in tumor microenvironment, modulating immune responses and so on.

Cordycepin has been widely recognized for its therapeutic potential against many types of cancers by numerous molecular mechanisms. It reduces inflammation, induces apoptosis, inhibits cancer cell proliferation, induces cell cycle arrest in cancer cells, and thus, kill or control cancer cell growth. Furthermore, cordycepin also inhibits tumor metastasis. What is surprising is the absence of toxicity of this metabolite. The researchers^{52,53} agree on the fact that cordycepin has excellent potential as a lead for drug development. In the last 3 years cordycepin is used in clinical trials in the form of a drug (ProTide NUC-7738) in various forms of cancer. In a phase I clinical trial NUC-7738 shows effective proapoptotic activity and strongly inhibits the NF- κ B pathway⁵⁴. In a phase I study on patients with advanced stage treatment-refractory advanced solid cancers, cordycepin (NUC-7738) has shown anticancer activities overcoming chemo-resistance and improving longevity and was well tolerated by the patients. These promising results support Cordycepin ProTide NUC-7738 further clinical evaluation⁵⁵ as a novel cancer treatment with almost no side effects in cancers and in chemoresistant advanced cancers.

Mushroom and mushroom beta-glucans supplementation in BC patients improve the overall response rate during conventional oncological treatments, reduce side effects, enhance immunity, speed up recovery, and improve QoL⁵⁶. Moreover, the potential to interfere with processes involved in the development or control of

cancer makes whole Med Mush and mushroom metabolites interesting candidates as adjuvants in antitumor therapies as well as in cancer prevention strategies.

A Preclinical Study on Triple Negative Breast Cancer: a Medicinal Mushrooms Blend Exerts a Direct Anticancer Effect on Lung Metastases

Prof. Paola Rossi, Ph.D
Department of Biology and Biotechnology “L. Spallanzani”, University of Pavia, Pavia, Italy

Complementary and integrative medicine (CIM) is becoming an increasingly popular and visible component of oncology care. Recently, the use of mycotherapy, a type of CAM, has been associated with positive impacts in cancer patients in terms of responses to treatment, reductions in side effects, and improvements in QoL. Medicinal mushroom extracts have been proposed as promising anti-cancer agents, but the mechanism of action on metastatic BC are still to be clarified. We published a first paper, a systematic review, with the purpose to evaluate the clinical effects of mycotherapy (specifically, the use of *Ganoderma lucidum* and *Grifola frondosa*) on long-term survival, tumor response, host immune functions, and QoL in cancer patients²⁹.

Then, with two research papers we exploited the effect of a novel Med Mush blend, namely *Micotherapy U-care*, in a 4T1 triple-negative syngeneic mouse BC model⁵⁷. Mice were orally administered with a mixture of *Agaricus blazei*, *Ophiocordyceps sinensis*, *Ganoderma lucidum*,

Grifola frondosa, *Lentinula edodes*. The syngeneic tumor-bearing mice were generated by injecting 4T1 cells in both supplemented and non-supplemented mice. After sacrifice, 25 days later, specific endpoints and pathological outcomes were evaluated. In particular, the number and the density of pulmonary metastasis significantly decreased and the QoL improved. We evaluated some biomarkers of the murine pulmonary tissue both on metastatic area and on tumor microenvironment. In particular, immunohistochemically assessment of TGF- β 1, IL-6 and NOS2, COX2, SOD1 as markers of inflammation and oxidative stress were performed. Our results indicate that inflammatory and oxidative stress biomarkers decreased in a significantly manner both on and on metastatic area and on tumor microenvironment. Our first conclusion is that supplementation with this Med Mush blend, produced a striking reduction of lung metastases density/number, paralleled by decreased inflammation and oxidative stress both in in the tumor microenvironment and metastases, together with QoL amelioration.

We hypothesized that these effects could be due to either a direct anti-cancer effect and/or to a secondary/indirect impact of Micotherapy U-Care on systemic inflammation/immunomodulation. To address this question, we presently focused on apoptosis/proliferation, investigating specific molecules, i.e., PARP1, p53, BAX, Bcl2, and PCNA, whose critical role in BC is well recognized. We revealed that Micotherapy U-Care is effective to influence balance between cell death and proliferation, which appeared strictly

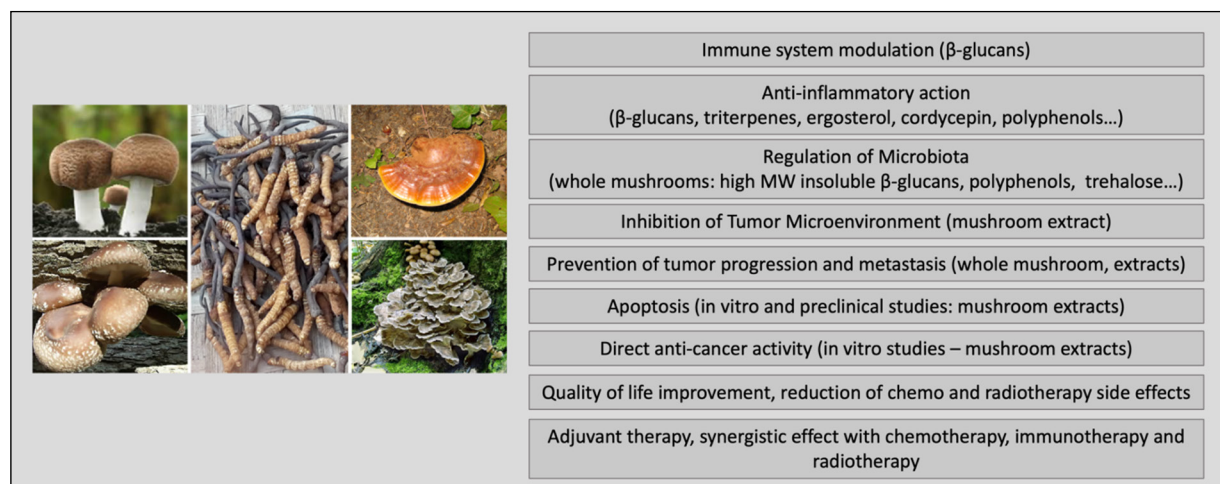


Figure 1. Principal biological effects of medicinal mushrooms demonstrated in different models of integrative oncology.

interconnected and inversely related (p53/Bax vs. Bcl2/PARP1/PCNA expression trends). Med Mush blend displayed a direct effect, with different efficacy extent on cancer cells and TME, forcing tumor cells to apoptosis⁵⁸. Yet again, this study supports the potential of Med Mush extracts, as adjuvant supplement in the TNBC management.

In conclusion, these findings support the valuable potential of *Micotherapy U-care* as support therapy in the critical management of TNBC.

Conclusions

The CIM has a key role in the management of breast cancer patients and is desirable that this kind of approach is shared between physicians and patients⁵⁹⁻⁶².

Unfortunately, the lack of CIM knowledge by physicians and their limited communication with patients have negative consequences and implications for clinical management and outcomes³⁴. Moreover, it has been demonstrated that the use of alternative medicine, instead of CM and out of CIM approach, was associated with worse five-year survival in cancer patients.

In conclusion, we believe that CIM approach, within a multidisciplinary team, represents a valid option to improve the QoL in cancer, chronic and so called frail-patients⁶³⁻⁶⁶.

In the next future, our wish is to propose and organize prospective studies, within the IMRG, with the aim to improve the knowledge of various categories of patients, treated within a program of multidisciplinary and integrative approach.

Conflict of Interest

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

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Scientific Manager of the Event

Prof. Massimiliano Berretta, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, and Dr. Pier Paolo Zanello PhD, AVD Reform Scientific Manager, Noceto, Parma, Italy.

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