ISTITUTO SUPERIORE DI SANITÀ

First ISS-ARTOI Conference on Integrative Oncology
Fifth ARTOI International Congress

Translational medicine: from the laboratory to clinical evidence

Istituto Superiore di Sanità
Rome, November 6-7, 2013

ABSTRACT BOOK

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ISSN 0393-5620
ISTISAN Congressi
13/C4

Istituto Superiore di Sanità
First ISS-ARTOI Conference on Integrative Oncology; Fifth ARTOI International Congress. Translational medicine: from the laboratory to clinical evidence. Istituto Superiore di Sanità. Rome, November 6-7, 2013. Abstract book.
Edited by Massimo Bonucci, Stefania Meschini and Annarita Stringaro
2013, ix, 71 p. ISTISAN Congressi 13/C4

The international conference has been organized by the Department of hematology, oncology and molecular medicine, Department of infectious, parasitic and immune-mediated diseases, Department of technology and health, Department of therapeutic research and medicine evaluation in collaboration with the Research Association for Integrative Oncology (ARTOI). The primary aim of this conference was to devote two days to the study, the research and the application of anticancer treatments based on the integrative use of multiple therapeutic options. The conference was held over two days and was divided in four sessions: cancer prevention, integrative oncology research, integrative therapy in oncology, integrative approach to cancer care: case studies. The most expensive cancer therapies have not always proved to be the most effective. The results obtained with the use of integrative cancer therapies have favoured, in some cases, the optimization of the associated therapy with a satisfactory reduction of costs for the National Health Service.
Key words: Oncology, Prevention, Integrative Therapies, Translational Research

Istituto Superiore di Sanità
Primo convegno Oncologia Integrata ISS-ARTOI; Quinto Convegno Internazionale ARTOI. Medicina traslazionale: dal laboratorio all'evidenza clinica. Istituto Superiore di Sanità. Roma, 6-7 novembre 2013. Riassunti.
A cura di Massimo Bonucci, Stefania Meschini e Annarita Stringaro
2013, ix, 71 p. ISTISAN Congressi 13/C4 (in inglese)

Il congresso internazionale è stato organizzato dai Dipartimenti di ematologia, oncologia e medicina molecolare, farmaco, malattie infettive, parassitarie ed immunomediate e tecnologie e salute in collaborazione con l'Associazione di Ricerca per le Terapie Oncologiche Integrate (ARTOI). Scopo primario di questo congresso è stato quello di dedicare due giornate allo studio, alla ricerca e all'applicazione di trattamenti oncologici operati attraverso l'uso integrato di più opzioni terapeutiche. Il congresso, svoltosi in due giornate, ha previsto l'intervento di relatori nazionali ed internazionali. Esso si è articolato in quattro sessioni: cancer prevention, integrative oncology research, integrative therapy in oncology, integrative approach to cancer care: case studies. Le terapie oncologiche più costose non sempre si sono rivelate le più efficienti: i risultati ottenuti con l'impiego delle terapie oncologiche integrate in alcuni casi hanno favorito l'ottimizzazione della terapia con una soddisfacente riduzione dei costi per il Servizio Sanitario Nazionale.
Parole chiave: Oncologia, Prevenzione, Terapie integrate, Ricerca Traslazionale

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Il rapporto è disponibile online sul sito di questo Istituto: www.iss.it

Citare questo documento come segue:
Bonucci M, Meschini S, Stringaro A (Ed.). *First ISS-ARTOI Conference on Integrative Oncology; Fifth ARTOI International Congress. Translational medicine: from the laboratory to clinical evidence. Istituto Superiore di Sanità. Rome, November 6-7, 2013. Abstract book.* Roma: Istituto Superiore di Sanità; 2013 (ISTISAN Congressi 13/C4).

Presidente dell'Istituto Superiore di Sanità e Direttore responsabile: *Fabrizio Oleari*
Registro della Stampa - Tribunale di Roma n. 131/88 del 1° marzo 1988 (*serie: Rapporti e congressi ISTISAN*)
Redazione*: Paola De Castro, Egiziana Colletta* e *Patrizia Mochi*
La responsabilità dei dati scientifici e tecnici è dei singoli autori.

Viale Regina Elena, 299 – 00161 Roma

Comitato Scientifico:
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Si ringraziano per il loro contributo incondizionato:
Interrnazionale Biolife srl, Imgep s.r.l. (Istituto di medicina genetica personalizzata), Imbio s.r.l. (Istituto di Medicina Biologica), Natur s.r.l., Allgeco Società consortile per Azioni, Diapath S.p.A, Biogroup s.r.l., CredSec S.p.A., Ghimas S.p.A., Andromedic s.r.l., Weleda Italia s.r.l., Coop Scia Servizi Cure integrate avanzate, Eurodream s.r.l., Villa Annamaria s.r.l., Eye Tech s.r.l., Mediterranea Servizi globali s.a.s. (Santa Candida grano Khorasan), OH Int.Le s.r.l., Farmacia Arrigoni, Farmacia Madre del Buon Consiglio Dott. Massimo Romiti, Bio Farmex s.r.l., Associazione Amici di Carlo Onlus.

Si ringraziano:
Maria Letizia Bertollini, Monica Brocco**,** Rossella Di Nallo, Veronica Michetti della Segreteria organizzativa, per il loro contributo alla realizzazione del Convegno.

Si ringraziano:
Daniela Casale e Federica Mosti per l'assistenza tecnica e per il lavoro di editing.

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Fabrizio Oleari
President of Istituto Superiore di Sanità
Massimo Bonucci
President of Associazione Ricerca Terapie Oncologiche Integrate
Pietro Bartolini
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Stefano Vella
Department of Therapeutic Research and Medicine Evaluation, Istituto Superiore di Sanità

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CANCER PREVENTION

Chairs: **Carla Fiorentini, Stephan Sagar**

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NOTES FOR THE READER

The book contains the abstracts of the oral and poster presentations at the "First ISS-ARTOI Conference on Integrative Oncology; Fifth ARTOI International Congress, Translational medicine: from the laboratory to clinical evidence".

Oral presentations follow the Programme. Posters appear under their first author in alphabetical order.

First session

Cancer prevention

Chairs

Carla Fiorentini, Stephan Sagar

THE DYNAMICS OF THE MULTI-DISCIPLINARY APPROACH IN CANCER

Philip Salem
Director Cancer Research Program St. Luke's Episcopal Hospital, Houston, USA

The multi-disciplinary approach is extremely significant in the design of the treatment strategy in cancer. This approach is a dynamic process that begins with making the diagnosis and ends with the cure, or death, of the patient. At the time of initial diagnosis, multiple consultations with expert pathologists should be obtained. This is not only to confirm the diagnosis, but also to make certain that the exact nature and biological profile of the cancer are delineated. This is particularly important when the clinical presentation of the disease does not coincide with the pathological diagnosis. After the diagnosis is confirmed, the process of staging starts. Also, here multiple consultations with diagnostic radiology and pathology should be made to determine the exact stage of the disease. Treatment should never begin before the diagnosis is confirmed and stage is determined. Prior to treatment a group consultation must be obtained with diagnostic radiology, pathology, medical oncology, surgical oncology and radiation oncology. This specific multi-disciplinary consultation should be done while all the experts are physically present at the same time. During this consultation the experts review the imaging studies, pathology, laboratory studies together, and design the treatment strategy. This strategy should only be delineated after such a group consultation. A common problem is that these multi-disciplinary consultations are usually done sequentially whereby the patient sees every expert alone. This is not the proper way of implementing the multi-disciplinary approach. The expert group who formulates the strategy of therapy should reconvene regularly at every turn of treatment and after completing every phase of therapy. At all times they should be posted as to the progress of the patient. The key to the success of the multi-disciplinary approach is to make certain that there is one leader for the group, and that leader should be the treating physician who assumes responsibility for the care of the patient and for the implementation of the strategy of therapy. The major objective of the multi-disciplinary approach is to make certain that the patient receives the best treatment that provides him with the best chance for cure. Also this approach provides the patient with psychological comfort and peace as he has not only obtained a second opinion, but many more.

DIET RESTRICTION AND CANCER

Ettore Bergamini
Centro di Ricerca di Biologia e Patologia dell'Invecchiamento, Università degli Studi, Pisa, Italy

The beneficial effects of anti-aging caloric restriction against cancer are well established. Biological aging is a major risk factor of cancer. Hence, benefits of intervention on aging on cancer incidence and retardation are not surprising, but underlying mechanisms are still obscure. Data so far available indicate that caloric restriction may decrease oxidative stress by stimulating mitophagy and mitochondrial turnover and protect from cancer initiation. Furthermore, evidence was produced that caloric restriction may stimulate apoptosis and prevent accumulation of heavily mutation-loaded cells. In addition, caloric restriction may decrease growth factor levels and tumour promotion. As an interesting very promising feature, caloric restriction may enhance sensitivity of tumour cells to radiation therapy and radiomimetic agents. Anti-cancer benefit of caloric restriction appear to be additive with the anti-cancer benefit of other anti-aging interventions acting by different mechanism(s), like physical exercise, antioxidants administration and polyunsaturated fatty acids uptake, and may be enhanced by the use of a Dynamic Synergistic Intervention (DANI).

DIET INFLAMMATION AND COLORECTAL CANCER, WHEN MUTUALISM BREAKS

Marco Candela (a), Elena Biagi (a), Silvia Turroni (a), Simone Rampelli (a), Franck Carbonero (b), Carla Fiorentini (c), Patrizia Brigidi (a)
(a) Università degli Studi, Bologna, Italy
(b) University of Arkansas, Fayetteville, USA
(c) Dipartimento del Farmaco, Istituto Superiore di Sanità, Rome, Italy

The worldwide diffusion of NGS-based microbiota surveys in CRC patients, alongside the utilization of germ free, monoassociated and humanized mice, led to an increasing perception of the pivotal role exerted by gut microbiota in CRC onset and progression. The microbial ecology of the process has been disclosed, and lights on the mechanisms involved have been shed. This brought the researchers to focus their attention on triggering factors that turn the intestinal microbiota from a mutualistic configuration to a CRC-promoting asset. Inflammation has undoubtedly a central role in this process, being a common outcome shared by different triggering factors such as diet, aging, microbe-microbe and microbe-host interactions. In particular, changes in diet, aging, as well as pathobionts-dependent pro-inflammatory dysbioses of the gut microbiota, can force gut microbiota to a pro-inflammatory asset, changing the microecology of the gut ecosystem and activating toxigenic bacterial CRC drivers. In this context, of extraordinary importance will be the development of strategies to interfere and/or block this triggering factors, preserving microbiota-host mutualism along the entire lifespan. Different approaches can be implemented. Since diet represents the pivotal strategy to modulate composition and function of the gut microbiota, the most promising ones rely on dietary interventions. For instance, diet can be modulated to boost health promoting microbiota groups, such as anti-inflammatory members of the Clostridium cluster IV or short chain fatty acids producers of the Clostridium cluster XIVa. Supporting this thesis, in a life-long longitudinal study carried out on mice successfully demonstrated that different diets modulates differently the microbiome trajectories along with aging. However, even if significant steps forward in the compression of the microbiome role in CRC have been carried out, more longitudinal microbiome surveys need to be carried out, following the microbial dynamics along time for the development of colonic neoplasia. Meta-analysis integrating epidemiological studies with microbiome data sets will be performed, allowing to better define triggering factors that force the microbiota to become carcinogenic, so that hypothesis can be verified on mice where possible intervention strategies can be tested.

PAP-BREAST: A NEW PROGRAM FOR BREAST CANCER PREVENTION

Gianluca Pazzaglia
Bresting Center, Perugia, Italy

PAP-BREAST is an assessment test for the risk of developing breast cancer. The patient will know from the results of the test if it is more or less high the probability of developing the disease. Like the Pap test for cervical cancer, PAP-BREAST allows the assessment of the risk of developing breast cancer. Until now, all executables investigations, i.e. mammography, ultrasound, MRI, or the latest tomosintesi (a kind of three-dimensional mammography), etc. were oriented toward the past. The investigation day used to be the checkpoint of what happened since the previous control. Today instead we begin to look forward, because understanding what is the breast risk profile make us capable of trying and planning interventions to effectively reduce the risk. Over the years Pap Test for cervical cancer has been a successful screening method because it is capable of detecting pre-cancerous lesions, that is alterations that untreated might over time turn into cancer. Mortality from cervical cancer dropped abruptly since the advent of the Pap Test. We cannot affirm the same about breast cancer. However, even in the case of breast cancer, pre-cancerous changes can be identified and their evolution is comparable to the one of uterine cervix lesions. These alterations are developed many years before the cancer nodule becomes visible through the mammogram and the ultrasound. In the Pap Breast a special equipment allows the release and sampling of secretion from the nipple of the breast. The secretion is than examined, and an health indicator is chosen, which in turn correlates with a risk profile. Women who do not produce any secretion are called “normal” (relative risk of developing cancer = 1: This is the basal value), whilst for women who produce secretion there is a scale ranging from 0 to 4:

- Category 0: secretion with normal cells number ranging from 0 9 (risk = 1.05-1.4);
- Category 1: secretion with normal cells number higher than 10 (risk = 1.8-2.27);
- Category 2: secretion with proliferation cell (hyperplasic) (risk = 2.5);
- Category 3: secretion with unnormal cells (atypical) (risk = 4.9);
- Category 4: secretion with suspicious cells (risk = 15-17).

From an operational point of view patients can be grouped into two categories:

- Category A non-significant risk: absence of secretion + category 0 + category 1;
- Category B higher risk: category 2 + category 3 + category 4.

Where results highlight high-risk patient the following advices are given:

- increased frequency of traditional imaging studies (mammography, ultrasound, tomosynthesis, magnetic resonance imaging);
- prescriptions related to lifestyle for prevention;
- other options such as drug treatments or eventually surgery.

DIETARY FATTY ACID AND ADIPOSE TISSUE FUNCTION IN COLON CANCER

Massimo D'Archivio (a), Beatrice Scazzocchio (a), Stefania Giammarioli (a), Maria Fiani (b), RosariaVarì (a), Carmela Santangelo (a), Augusto Veneziani (c), Annunziata Iacovelli (d), Claudio Giovannini (a), Sandra Gessani (b), Roberta Masella (a)

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The increasing prevalence of obesity worldwide poses a great challenge to global health as obesity not only represents a main risk factor for chronic degenerative diseases, but it can also increase the incidence of many cancers including Colorectal Cancer (CRC). A critical barrier to progress into the field is represented by the still poor knowledge on how adipose tissue metabolism can impact cancer development. White Adipose Tissue (WAT) is a complex immunocompetent organ, composed of different cell types among which adipocytes and resident immune cells, exhibiting secretory and regulatory activities. Obesity disrupts the dynamic role of these cells altering the adipokine signaling, and increasing the levels of inflammatory cytokines responsible for the activation of transcription factors such as STAT3, constitutively expressed in many tumors. Dietary components may influence the inflammatory process and the risk of developing CRC. Fatty Acids (FAs) are key WAT components and, given their precursor status to signaling lipid mediators, major determinants in inflammation. The opposite behaviors of ω3- (anti-inflammatory) and ω6- (pro-inflammatory) polyunsatured-FAs in modulating several adipose and immune cell functions have been demonstrated. FAs could contribute to maintain the proper balance of key transcriptional regulators, thus controlling the inflammatory response of adipocytes. In particular, Docosahexaenoic Acid (DHA) exerts a strong anti-inflammatory activity. To test the hypothesis that WAT represents the initial place where dietary FAs influence inflammation, we defined the inflammatory status and specific FA profiles of WAT associated with CRC. To assess the role of changes in WAT FA profiles in tissue inflammation, we compared ω3- and ω6-FAs content and the inflammatory status of adipocytes isolated from WATs of normal-weight and overweight/obese individuals affected or not by CRC. We provided evidence for a pro-inflammatory environment in WAT of CRC patients, as assessed by the up-regulation of STAT3, and the concomitant decrease of PPARγ and adiponectin with respect to healthy subjects. This imbalance was correlated with a decreased ω3-/ω6-PUFA ratio and was independent of obesity degree, suggesting that qualitative changes, other than quantitative ones, in WAT FAs may influence tissue dysfunctions. This hypothesis was further supported by the finding that adipocyte treatment with DHA restored the equilibrium between STAT3 and PPARγ.

Second session

Integrative oncology research

Chairs

Giampiero Ravagnan, Filippo Belardelli

MULTI-TARGETING OF MULTIGENIC CANCER BY NUTRACEUTICALS: ROLE IN PREVENTION AND TREATMENT

Bharat B. Aggarwal
Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas, MD Anderson Cancer Center, Houston, Texas, USA

Extensive research within last decade has revealed that most cancers are caused by alteration in multiple genes. Thus mono-targeted therapies as being used currently are not only highly expensive but also are unlikely to prevent or treat most cancers. According to some estimates as many as 80% of all therapeutics currently being used against cancer, have their roots in natural products. the latter tend to be safe, affordable and multi-targeted. our group has identified over 50 different compounds from traditional medicine and from dietary agents, normally called nutraceuticals that can modulate various cell-signaling pathways linked to most cancers. We will present the evidence that pro-inflammatory pathways linked to transformation, survival, proliferation, invasion, metastasis, chemoresistance, and radioresistance of tumors can be downregulated by these nutraceuticals through suppression of pathways leading to activation of nf-kb, stat3, cxcr4, cox2, bcl-2, bcl-xl, xiap, survivin, mmp-9, vegf, cyclin d1, c-myc and rankl. both *in vitro* and *in vivo* evidence will be presented that nutraceuticals have a potential both to prevent and treat most cancers.

NATURAL ALKALOID PRODUCTS: DRUG DISCOVERY AND THERAPEUTIC OPTIMIZATION

Maria Condello (a,b), Dario Cosentino (a), Silvia Corinti (c), Gabriella Di Felice (c), Giuseppina Multari (d), Francesca Romana Gallo (d), Giuseppe Arancia (a), Stefania Meschini (a)

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A number of successful systemic therapies are available for the treatment of metastatic cancer. Unfortunately, the tumor response is often transient, and therapy frequently fails for the appearance of resistant cell populations. Tumors usually consist of mixed populations of malignant cells, some of wich are drug-sensitive while others are Multidrug Resistant (MDR). The identification of molecular targets in drug resistant cells can lead to the development of new therapeutic combinations to hit in a differentiated way the heterogeneity of tumor cells. Use of natural products for cancer treatment has been extensively documented, playing an essential role in healthcare. Several alkaloids isolated from natural plants exhibit antiproliferative and antimetastatic effects on various types of cancer both *in vitro* and *in vivo*. Some of them, camptothecin, vinblastine and vincristine, are anticancer drugs with well defined clinical uses exerting their action on microtubules dynamics, on mitochondria activities and DNA replication. In our previous studies, the bisindolic Alkaloid Voacamine (VOA), isolated from the Peschiera fuchsiaefolia plant, exerted a chemosensitizing effect on cultured MDR osteosarcoma cells (U-2 OS/DX) exposed to Doxorubicin (DOX). Pretreatment with VOA, at noncytotoxic concentrations, inhibited P-gp action in a competitive way, accounting for the enhancement of intracellular content and cytotoxic effect of DOX induced on MDR cells. In this work, using a different osteosarcoma cell line (SAOS-2-DX), and a melanoma cell line (Me30966) intrinsically drug resistant and P-gp negative, we have shown the ability of VOA to sensitize cancer cells of different histological origin. An important concern regarding the use of natural products in combination with chemotherapeutic agents, is their interaction with different biological systems, with particular attention to the immune system. *In vitro* preliminary results obtained on mouse Bone Marrow-Derived Dendritic Cells (BM-DC), showed that VOA neither directly affected their maturation nor had an effect on LPS-induced maturation, indicating the absence of intrinsic immunotoxic and inflammatory properties of the plant alkaloid. These findings suggest promising clinical applications of this natural substance in integrative oncologic therapies against resistant tumors.

POTENTIAL THERAPEUTIC ACTIVITY OF TEA TREE OIL AND ITS MAIN COMPONENT, TERPINEN-4-OL, AGAINST MUCOCUTANEOUS CANDIDIASIS IN ONCOLOGY

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Anti-cancer therapies may cause severe infections owing to the toxicity and immunodepressive effects of radiation and/or drugs used to control the neoplastic cell spread. Mucocutaneus fungal infections, caused mainly by opportunistic *Candida* species, are common in cancer patients, and are usually limited to mucocutaneous sites. In addition, the lack of cooperation by the immune system often results either in partial therapeutic efficacy or in resistance to antifungal drugs, with worsening of disease burden. Moreover, the ability of *Candida Albicans* (CA), the main agent of mucocutaneous infection, to grow as hyphal biofilm further reduce the effectiveness of most antifungal agents. Finally, misuse of antifungal drugs may cause the emergence of resistant yeasts, particularly the selection of azole-resistant strains of CA. There is growing interest for natural products with the aim of developing new classes of antimicrobials to be used alone or in combination with conventional therapies, to prevent and /or improve treatment of established infections, and also limit further development of drug resistance, particularly among immunocompromised patients. The present study aimed to highlight the therapeutic potential of essential oils and phytoconstituents extracted from medicinal plants "anecdotally", though widely, used for the treatment of mucocutaneous fungal infections, focusing on the therapeutic properties of Tea Tree Oil (TTO) and its main component Terpinen-4-ol (TERP). TTO is steam distillated from the leaves of the Australian *Melaleuca alternifolia*. Studies have demonstrated anti-inflammatory and antimicrobial activities against a broad spectrum of microorganisms such as *Staphylococcus aureus*, coliforms and *herpes simplex* virus, which are common oral isolates of cancer patients. TTO also has potent activity against many fungi including some azole-resistant yeasts with evidence of efficacy in treating fluconazole refractory oral candidosis in AIDS patients, as reported by Mondello F. in 2003 and 2006 and Bagg J. in 2006. Moreover, TERP, the main TTO component, has shown antimicrobial properties. For its safety and consistency, TERP may be more appropriate for the development of oral care products. Overall, TTO and TERP could potentially prevent or treat mucocutaneous fungal infections thanks to their antimicrobial effectiveness, potential synergy with conventional antifungals, and reported low toxicity, together with promising data from pre-clinical studies. However further research and controlled clinical trials are required to determine the efficacy and risks of these plant-derived products in cancer patients.

ANTITUMOR ACTIVITY OF ALOE-EMODIN IN BREAST CANCER CELLS

Marisa Colone (a), Annarica Calcabrini (a), Emiliano Fratini (a), Pasquale Anello (a), Mariarosaria Tortora (b), Chiara Giuliani (c), Cecilia Bombelli (c), Francesca Cavalieri (b), Giovanna Mancini (c), Annarita Stringaro (a)

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With the aim of developing novel anticancer drugs characterized by selective targeting and low toxicity for normal dividing cells, we have devoted our attention to a number of natural compounds that have traditionally been used to treat a variety of diseases. We have assayed only those natural compounds showing no toxicity to normal cells, and we evaluated their efficacy against cancer cells. Aloe Emodin (AE), a natural hydroxyanthraquinone from Aloe vera leaves, is reported to have cytotoxic activity against various cancer cell lines. Interestingly, AE showed an affinity for human breast cancer. Our recent study clearly demonstrated the *in vitro* anti-proliferative effect of AE on the breast adenocarcinoma cell line SKBR3. Cancer cells were incubated with or without different AE concentrations for 24, 48 and 72 h. The morphological alterations were evaluated by Scanning Electron Microscopy (SEM). Cell viability assay (MTT test) showed that AE inhibited SKBR3 cell proliferation in a concentration-and time-dependent manner. Moreover, cell cycle was analyzed by flow cytometry to elucidate the mechanism of AE-induced cell growth inhibition. Cell cycle modifications and alteration of its regulatory proteins are frequently associated with induction of apoptosis. To determine whether AE activated apoptosis in SKBR3 cells, morphological and biochemical parameters were evaluated. Höechst staining and flow cytometric analysis of annexin V-FITC-positive cells showed that AE treatment induced apoptotic death in SKBR3 cancer cells. Studies are in progress to evaluate different drug delivery systems in order to increase antitumor AE efficacy on breast cancer, as model of solid tumor.

THE FRONTIERS OF RADIOSURGERY: FROM THE CYBERKNIFE TO SYNCHROTRON RADIATION

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Stereotactic Radiosurgery (SRS) is a radiation technique focusing with submillimetric precision high energy beams toward a clinical target. Originally developed to treat brain disease, SRS was limited by the need of a stereotactic frame immobilizing the head. The introduction of real time image-guidance based on amorphous silicon detectors, paired with a light-weight linear accelerator mounted on a robotic arm able to move synchronously with body movements, allowed the development of the Cyberknife. Cyberknife radiosurgery does not require immobilization of the body part treated, allowing the accurate delivery of ablative doses of radiation to targets in any part of the body. The fast spread of radiosurgery beyond the skull is witnessed by the growing number of patients treated and related publications worldwide. SRS is today still limited by the radiation doses given to the tissues adjacent the tumor. Synchrotron-generated microplanar beams (microbeams) provide a powerful new tool to substantially increase the radiation doses to the tumor (up to a level causing immediate cell death) while delivering minimal and well tolerated doses to nearby tissues. The non invasive ablation of tumors as well as the ability to modulate brain function with microscopic scale non invasive intervention open an exciting new field of application to treatment of tumors and other disorders.

ONCOGENOMICS AND PERSONALIZED MEDICINE

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In the last years, the scientific results obtained in the field of pharmacogenomics have opened a promising perspective in the development of "personalized medicine". Actually, in oncology area there are some examples of biomarkes that results useful to assess the therapy in the breast cancer (*Her2/neu over-expression*) and colon-rectum cancer (*EGFR expression with alternate context*). The development and use of biomarkers trigger the need to establish standards in the context of regulatory aspects. Pharmaceutical and diagnostic companies have recognized the importance and impact of genomic biomarkers, but also the complexity along biomarker development and have therefore decided to combine their efforts. Recent years have seen numerous initiatives promoted by governement bodies, institutions and associations designed to provide guidelines for the research and clinical application of predictive disease tests and therapy response tests. Also International Regulatory Agencies are working in the assessment process for predictive genetic tests in order to provide guidance about appropriate development paths, also in order to facilitate the research and development of biomarkers that can be useful not only for diagnosis of diseases, but also for understanding the pathogenesis of diseases, and to improve the efficacy and safety of therapies, facilitating the development of a personalized medicine.

Third session

Integrative therapy in oncology

Chairs

Massimo Fioranelli, Stefano Vella

ACUPUNCTURE IN CANCER CARE: THE US EXPERIENCE

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Most major cancer centers in the United States have established integrative medicine programs to address cancer patients' need of taking advantage of therapeutic modalities that have not been part of Western mainstream care - the complementary therapies. Acupuncture, originated from Traditional Chinese Medicine, is one of those modalities. Historically it was used in treatment of many ailments, yet its efficacy and mechanism of action are subjected to scientific research only in recent decades. The research efforts have generated an increasing amount of data that would guide clinicians in using acupuncture in the care of cancer patients. The data helps make acupuncture one of the most accepted complementary therapy modalities in the United States. In this presentation, Dr. Deng will review data from neuroscience research and clinical trials on acupuncture, describe its application in clinical practice in the setting of the US health care system, discuss progress achieved and obstacles encountered, and explore prospects of further integration with mainstream oncology practice.

INTEGRATIVE MEDICINE APPROACH TO PALLIATIVE CARE IMPROVEMENT

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In 2008, an Integrative Oncology Program (IOP), aiming to improve patients' quality of life during chemotherapy and advanced cancer, was launched within the Clalit Health Organization's (CHS) oncology service at the Lin Medical Center, Haifa, Israel. The IOP is based on a multi-disciplinary team that includes physicians and practitioners who are dually trained in conventional care as well as Complementary Medicine (CM). The IOP team provides a wide spectrum of traditional and CM modalities which include nutritional counseling (diet and supplements), herbal medicine, mind-body and touch therapies, acupuncture, Anthroposophic medicine, homeopathy and spiritual care. In the following lecture, we will present a research-based approach to integration of CM modalities within palliative care. Integrative oncology care in the palliative setting is aimed to enhance patients' quality of life and to reduce both patients' and care givers' concerns. Clinical indications to integrative oncology consultation in palliative care include pain, fatigue, gastro-intestinal symptoms (e.g. nausea, appetite loss, constipation), emotional and spiritual concerns (regarding QOL as well as quality of dying), insomnia, dyspnea, and symptoms related to current or previous chemotherapy adverse effects (e.g. neuropathy). CM modalities that are mainly integrated within palliative care include acupuncture, mind-body and manual healing modalities, Anthroposophic medicine including art therapies, and nutritional/herbal supplements.

THE BACTERIAL PROTEIN TOXIN, CYTOTOXIC NECROTIZING FACTOR 1 (CNF1) PROVIDES LONG-TERM SURVIVAL IN A MURINE GLIOMA MODEL

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Glioblastomas are largely unresponsive to all available treatments and there is therefore an urgent need for novel therapeutics. Here we have probed the antineoplastic effects of a bacterial protein toxin, the Cytotoxic Necrotizing Factor 1 (CNF1), in the syngenic GL261 Glioma Cell model. CNF1 produces a long-lasting activation of Rho GTPases, with consequent blockade of cytodieresis in proliferating cells and promotion of neuron health and plasticity. In cell culture experiments, we found that CNF1 was very effective in blocking proliferation of GL261cells, leading them to death within 15 days. CNF1 had a similar cytotoxic effect in human glioma cells obtained from surgical specimens. In *in vivo* experiments, we injected GL261 glioma cells into the adult mouse visual cortex, and five days later we administered either a single intracerebral dose of CNF1 or vehicle. To compare CNF1 with a canonical antitumoral drug, we infused Temozolomide (TMZ) via minipumps for 1 week in an additional animal group. Low dose (2 nM) CNF1 produced a survival effect, comparable to that of continuous TMZ infusion (median survival 35 days vs. 28 days in vehicle controls). Remarkably, increasing CNF1 concentration to 80 nM resulted in a dramatic enhancement of survival with no obvious toxicity. Indeed, 57% of the treated animals survived up to 60 days following GL261 glioma cell transplant. We conclude that activation of Rho GTPases by CNF1 represents a novel potential therapeutic strategy for the treatment of central nervous system tumors.

PATIENT-CENTERED INTEGRATIVE CARE: WHAT ARE THE CHALLENGES?

Stephen Sagar
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A patient centered-approach requires that patients be part of the joint-decision making process. This extends from an individual patient's anti-cancer management to more global decisons that contribute to clinical research and organizational values. Recognizing economic limitations, it is important that the public (as represented by patients and their associates) be involved in making vital decisions regarding the distribution of resources. Advantages include more self-responsibility, which is associated with better adherence to therapies, reduced adverse effects, less re-admittance to hospital, and improved long-term health outcomes. There are multiple barriers that prevent patients from making medical management decisions based on their own personal values and goals. These are patient-related, physician-related, and organization-related. Patients require education to an adequate knowledge level so that informed decisions can be made. They require time to contemplate their options and need access to a navigator who can support their search for options, evidence, and limitations of financial cost. The physician needs to be a teacher with excellent communication skills. With the support of an advanced practice nurse, options can be discussed that are in line with the patient's values and culture. Practitioners must be open to the patient's opinions, including use of complementary therapies when appropriate. It is the responsibility of the physician to discuss these options, not in a paternal fashion, but as a compassionate educator, explaining the evidence as it exists, discussing safety issues, but not discounting the patient's value system. Organizational barriers include top-down management that is not involved in front-line care. Institutional culture often dominates medical decisions on the front line of patient care. This may partly be based on economic and medico-legal issues. The organization determines the environment, staff stress, length of appointments, availability of supportive care, treatment options, and many other issues. Unfortunately, these are not always in the best interests of the patient. Guidelines from the Picker Institute are improving patient-centered care. Complementary therapies are only one part of integrative oncology. They have illustrated the importance of patients' values and led to some effective, evidence-based innovative techniques that fall outside of the conventional box. Integrative Oncology is a verb and not a noun. It is a process that allows a seamless and effective system that is supported by the organization to prevent patient passivity, encourage appropriate staff interaction, and enable the patient to be an important part of the team within a supportive and pleasant environment.

NATURAL PRODUCTS AND DRUG VIGILANCE

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Phytovigilance should be considered the twin of safety in herbal medicine especially in cancer patients. Herbs can give rise to many types of adverse reaction: allergy, hepatic or renal toxic reaction, chemotherapy interferences. Herbs can be contaminated by pesticides, aflatoxins, synthetic drugs and heavy metals. Many consumers do not even know that herbs can give rise to cancer. Nevertheless many people use herbs for prevention of diseases for years, almost always without any concrete medical control. Phytovigilance is still not recognized and fully granted as part of mainstream medicine; even collegues that consider herbal medicine a non sense often do not even consider their potential toxicities. During anamnesis still too few physicians ask on a regular basis patients if they are using herbal extracts. We are working from years on these issues to extend these knowledges to students and to professionals health care givers of all levels in the university school of medicine of Florence in masters, regular and ad hoc courses. From 10 years the ISS has set-up a National System of herbal pharmacovigilance to signal herb adverse reaction and a network of experts to fully evaluate them.

NOVEL STRATEGIES FOR COMBINING IMMUNOTHERAPY WITH CHEMOTHERAPY: FROM THE PRECLINICAL STUDIES TO THE CLINICAL EXPERIMENTATION

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More than a century of observation and research have shown that the natural responses of the organism, especially the immune responses, have a fundamental role in controlling the development of tumors. Because of its low toxicity and its specificity, immunotherapy may represent a biological tool in cancer therapy, complementary to current standard treatments (surgery, chemotherapy, radiotherapy). However, an obstacle is interposed between a good anti-tumor response and the eradication of the tumor itself. Such an obstacle is represented by "cancer immunoediting", a process through which the tumor, in its progressive development, mutes and blinds the immune responses making the organism tolerant to cancer development. Only the resetting of the immune system may allow to overcome this problem. Cyclophosphamide is a chemotherapeutic alkylating agent of the first generation widely used in various antineoplastic drug cocktails and considered immunosuppressive. Studies carried out in recent years have shown that cyclophosphamide has a amount of new features. In fact, it reduces the number of regulatory T cells (with immunosuppressive activity) but, above all, subsequently to its discontinuation, it induces a considerable production of immunostimulating factors (various types of interleukins and chemokines) which are responsible of a significant increase of the adaptive immunity leading to the the proliferation and activation of lymphocytes and to their migration in the tumor, as well as of the innate immunity with a subsequent raise in the frequency of dendritic cells. A therapeutic strategy based on a single injection of cyclophosphamide immediately followed by the administration of a tumor vaccine has been shown to induce significant tumor regressions in experimental models. This strategy, applied to patients undergoing surgery for melanoma metastases in a phase I study, gave similar results. Further studies are needed to define the optimal treatment modalities and the type of tumors susceptible, but the path traced allows us to consider this strategy as an effective tool to prevent relapses in cancer patients already freed from the primary tumor.

Fourth session

Integrative approach to cancer care: case studies

Chairs

Giuseppe Di Fede, Giovanni Rezza

TREATMENT RESPONSE TO ORALLY ADMINISTERED VISCUM ALBUM EXTRACT - PRELIMINARY RESEARCH IN A NEW THERAPEUTIC ROUTE FOR HEMATOLOGICAL MALIGNANCY

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In Integrative Oncology Viscum album treatment is a well known and brightly used treatment modality, mostly applicated as subcutaneous injection. Intravenous and intratumoral application is experienced more rarely. Data, published by the University of Bergen, Norge, referred to oral administration of mistletoe lectins and Viscum album extracts in animals and opened a new field of further research in humans. The presented data showed a dramatic dose-dependent hyperplastic growth of the small intestine in rats and mice feeded with mistletoe lectin I. Level of plasma TNFα and other cytokines increased significantly. Apoptosis in the tumors of animals was increased and in some cases complete tumor regression occured. Mistletoe lectins I, II and III stimulated the production of Immunoglobulin A and G. In a transplantated murine Non-Hodgkin lymphoma orally aplicated mistletoe lectin caused a dose dependent reduction of tumor weight. Our own data in 10 healthy volunteers orally treated with daily 200mg of an aqueous mistletoe extract from oak tree over a period of four weeks confirmed a time dependent increase of specific lectin I, II and III antibodies. In peripheral blood white blood cell count, neutrophils and lymphocytes increased at day 25 and showed a decline at the end of the experiment. These data encouraged the treatment of a 56 years old male with a atypic chronic lymphocytic leukemia. The patient denied subcutaneous injection, therefore oral treatment with an aqueous Viscum album extract from oak tree three times per week 200mg was initiated. It resulted in a normalization of peripheral blood count, the amount of prolymphocytic cells decreased and the soluble Interleukin-2 receptor level was reduced continuously. No other treatment took place. The enlarged lymphnodes became smaller. Quality of life was not decreased over the whole time before and after starting treatment. The oral intake of the extract had no side effects. In consequence other patients with chronic lymphocytic leukemia were treated orally with Viscum album and showed decrease in white blood count. A women with Non-Hodgkin lymphoma experienced complete remission of an egg-shaped ingiunal lymphnode by oral mistletoe treatment. These data for the first time prove adsorption and effectiveness of orally applicated Viscum album and necessarily justify further clinical research.

ACUPUNCTURE AS A COMPLEMENTARY THERAPY FOR CHEMOTHERAPY SIDE EFFECTS: THE EXPERIENCE OF A PUBLIC HEALTH SERVICE IN AOSTA VALLEY AUTONOMOUS REGION

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Cancer and treatment for cancer can cause a variety of symptoms, not all of which are appropriately managed with medical therapy. Val d'Aosta Autonomous Region in 2003 programmed an experimental project and the acupuncture service was offered to neoplastic patients to complement their on going therapies. One goal of the project is related with transferability of models of integrative health care in the context of the Italian National Health Service (SSN), and its impact deals with ensuring equitable access to appropriate and efficacious types of unconventional medicines for socially relevant pathological problems. A retrospective survey was carried out of the medical records of all patients treated with acupuncture from May 2003 to July 2013. The results of this study will be illustrated. Acupuncture is one complementary treatment with relatively few risks and side effects. One of cancer therapy side effects is oral mucositis that remain a major source of illness despite the use of a variety of agents to prevent them. Oral mucositis represents a major non-hematologic complication of cytotoxic chemotherapy and radiotherapy associated with significant morbidity; pain, odynodysphagia, dysgeusia, and subsequent dehydration and malnutrition reduce the quality of life of affected patients. The incidence and severity of oral mucositis is influenced by the type of antineoplastic treatment administered and by patient-related factors. From the literature we know that severe courses of oral mucositis are observed during simultaneous radiochemotherapy, which affects virtually all patients with head and neck cancer who receive this therapeutic modality. However, up to 40% of patients treated with conventional chemotherapy and the more than 70% of patients undergoing conditioning therapy for bone marrow transplantation also experience oral treatment-related complications. We'll present also the result of an observational study, conducted in the Acupuncture Clinic of Aosta Valley Regional Hospital, on the effect of acupuncture in the prevention and treatment of oral mucositis.

HOMEOPATHY IN TREATING MENOPAUSAL SYMPTOMS IN SURGICALLY RESECTED BREAST CANCER PATIENTS: A RANDOMIZED PHASE II-III TRIAL

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Background. Menopausal symptoms significantly impact quality of life in young women with breast cancer history and common substitute hormonal therapies are strongly contraindicated in these patients.

Materials and methods. Trial was conducted in two phases:

- Phase II: Pilot phase II study enrolled 10 patients to assume homeopathic treatment Klimaktoplant DHU (1 cap, dosage 0,25 g containing Cimicifuga D2 25mg, Sepia D2 25mg, Ignatia D3 25mg, Sanguinaria D2 25mg), sub-lingual, days 1-90;
- Phase III: Randomized Phase III trial to compare sub-lingual homeopathic treatment versus placebo for 6 months. 35 patients have been enrolled and 31 of them completed the course.

Menopausal symptoms (including but not limited to hot flushes, sweat, insomnia etc.) have been evaluated using NCI-CTC scale at two time points: time 0 (basal visit) and time 1 (after 3 months treatments) for patients already enrolled in Phase II study, or after 3 and 6 months therapy respectively for newly enrolled patients. Main objective was to evaluate efficacy and tolerability of a complex homeopathic schedule in the treatment of menopausal symptoms in surgically resected breast cancer patients.

Results.

- Phase II: 78 different symptoms have been recorded for whom 57 reductions of at least 1 point score (73%), 17 stability (21.8%), 4 increase of at least 1 point score (5.2%) have been obtained. All symptom scores have been summed up to obtain a single global score per patient per time point. A significant reduction in symptoms and a statistically significant reduction in scores have been observed for all patients (paired data t test, $p<0,001$);
- Phase III: A significant reduction in global score at time 1 versus time 0 has been observed in patients receiving homeopathic treatment (Wilcoxon Signed Rank test, $p=0,0185$).

Conclusions. Results obtained from this Phase II/III trial have demonstrated efficacy and safety of homeopathic treatment in the cure of menopausal symptoms in a subset of patients that could have not benefited of substitute hormonal therapies.

INTEGRATIVE TREATMENTS IN CANCER PATIENTS: CASE STUDIES

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Introduction. The tumor is still a disease not completely eradicated. Often we can have good results for hematologic malignancy, but we have not in the solid tumor. If we consider brain tumors then we realize that our hopes to have positive results are really very small. That's why all the efforts in finding new therapeutic approaches must always be taken into account. We know that some natural substances have the ability to block proliferation genes neoplastic brain, COX-2 and 5-LOH, blockade of angiogenesis, activation of apoptosis, stimulation of the Immune System. Moreover, the substances in question have the ability to pass the BBE and then to carry out their action, even in brain cells. These substances are the Boswellia Serrata, Curcumin phospholipid, the polydatin, alpha-and beta-glucans, the Ruta and Calcarea Sulphur (low-dose).

Results. This phyto-homeopathic treatment in combination with an antineoplastic drug (Temozolomide) has led to very encouraging results in cases of glioblastoma multiforme and malignant oligodendroglioma. After radiotherapy and/or Cyberknife continued use of medical therapy and phyto-homeopathic contributed to the disappearance of intracranial lesions and to maintain this disappearance for a period of 24 months in a case of glioblastoma and 6 years in the case of oligodendroglioma malignant.

Conclusions. The brain tumors often have a poor prognosis in a short time. There are currently no protocols that ensure a long survival. The use of natural substances of which we know the scientific properties, in combination with standard protocols could be considered as a further opportunity for the patients suffering from these diseases.

INTEGRATIVE APPROACH WITH DIET AND COMPLEMENTARY MEDICINE IN ONCOLOGY. THE EXPERIENCE IN THE HOSPITAL OF LUCCA (ITALY)

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Aim. We report our experience with the use of complementary therapies and diet in patients with solid tumors during and at the end of anticancer treatment. It is important to provide qualified and evidence based information on the role of diet to reduce some side effects of chemotherapy such as dysgeusia and during anti hormonal therapies, especially in hormone responsive breast cancer treatment such as water retention and weight gain.

Methods. Patients access to the clinic making an appointment by CUP phone. In the clinic they meet medical doctors expert in nutrition and complementary medicine. The indications to complementary treatments include administration of a low-carbohydrate diet designed for patients with hormone responsive Breast Cancer (BC) in antiestrogen or antiaromatase therapy, particularly in those patients who developed moderate or severe Nonalcoholic Steatohepatitis (NASH), increased transaminases and altered lipid profile. Pre-defined simple protocols to reduce side effects of anticancer therapies, indication of sessions of acupuncture/homeopathy to decrease side effects of chemotherapy/radiotherapy and antihormonal treatments such as hot flashes in order to improve the quality of life are also applied.

Results. From the end of October 2010 till April 2012 (18 months), 89 patients have been visited (12 male and 77 female); the average age is 56 (32-88) years; 61 patients with breast cancer, 6 gynecologic cancer, 8 gastro-intestinal cancer, 2 head and neck cancer, 3 prostate cancer, 1 brain cancer, 4 NSCLC and 4 hematologic cancer. 23 patients had already metastasis. 40% of patients asked for information about CAM and their "role" in reducing anticancer therapy side-effects. 10% of patients were using CAM for other purposes before cancer diagnosis and needed to continue during anticancer treatments. Most of them are women with high level of education. 17% of patients were using "heretic therapy" in particular 3 patients were taking Cuban scorpion venom (Vidatox or Escozul) together with hormonal treatment. In particular, moderate physical activity was recommended especially to women in treatment for early breast cancer (EBC). It was recommended a food frequency diary to register body weight weekly.

Conclusions. An improvement in the quality of life was observed with decreased fatigue, anxiety and depression. Patients who followed a diet therapy have shown weight loss with better lipid profile and decrease in liver tests of NASH**.** Homeopathy significantly improved the subjective measures of hot flash frequency and severity, mood, fatigue, and anxiety. Acupuncture improved hot flash frequency and vasomotor symptoms.

THE DIGITAL MEDICAL RECORD AND VIDEOCONFERENCE FOR THE PATIENT: JUST A CLICK AWAY FOR INTEGRATIVE CONSULTING

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Telemedicine is known as an improvement in the quality of health care. It allows the accessibility of care, diagnostic services and medical advice from a distance, as well as constant screening of vital parameters, all in all reducing the risk of complications in populations at risk or suffering from chronic diseases. Considering the emerging "aging population" and the increase in chronic diseases, healthcare through the network can be synergistic, with telemedicine, also in the process of prevention. ARTOI considers telemedicine as part of a larger project, such as the organization of medical records history of the patients in the network, through the use of cloud computing. This leads to easier and faster availability of clinical data and resulting monitoring of the health status of the population. Specifically, referring to ARTOI, this can give statistical indications in cancer therapies. This will be the starting point in order to integrate all the NHS in a large computer network which will eventually provide a possibility to store and record the analytical data (clinical, laboratory examinations, diagnosis and treatment) in a chronological and stanadard schedule, leading to a reduction in public spending (unnecessary repeats of clinical examinations will be prevented). Access to the cloud by the physician follows the norms on the protection of privacy and allows controlled sharing of patient data among several physicians. The system can also function as a platform managing medical video conferences and, on top of everything, the open system can differentiate into:

- telepathology;
- teleradiology;
- telecardiology;
- teledermatology;
- tele-rehabilitation;
- remote medical consultation.

CARE MODELS AND INFORMATION AND COMMUNICATION TECHNOLOGY IN FAVOUR OF LONG-TERM SURVIVORS

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Given the increasing incidence of chronic diseases across the world, the search for more effective strategies to prevent and manage them is essential. The use of care models adapted to the characteristics of the patient and based on an appropriate use of available resources, proved to be very effective not only for the prevention of many diseases, but also for rehabilitation. The most effective interventions for improvements in chronic disease care were found to be based on the combination of multi-pronged strategies. This concept has been completely taken within the scheme of the Chronic Care Model (CCM), largely based on the clinical guided exploitation of the territorial resources, and considered to be effective in facing the growing challenge of chronic diseases. Proponents of the CCM have suggested that it can also be used for the prevention of chronic disease. Glasgow (2001) theorize that change will be less costly and more effective if both clinical prevention and management of chronic disease use a similar set of improvement strategies. With recent improvements in the early detection, diagnosis, and treatment of cancer, people with cancer are living longer, and cancer can be thus considered and partly managed as a chronic illness. Both Ictus and Cancer patients could be then viewed as long survivors with similar rehabilitation needs and in a quest for an acceptable quality of life (QOL). Concepts used in Adapted Physical Activity (APA) program could be useful also in the chronic management of oncological patients. CCM in oncology was already designed to give new possibility to the empowered patients. As a chronic illness, cancer care occurs on a continuum that stretches from prevention to the end of life. This is a useful paradigm for planning and testing interventions for improving clinical outcomes and enhancing patient's QOL. To start with, the appropriate methodology was considered to implement a chronic care model in a regional context (e.g. ASL): for this purpose APA was considered at first as a case study, based on the already successful realization in Italy and USA, within the process for the implementation of a CCM for chronic stroke survivors. Then, the extension to oncology rehabilitation of the CCM methodology was addressed, together with a review of the most appropriate ICT solutions for this particular application.

Poster

ATRIAL NATRIURETIC PEPTIDE: A MAGIC BULLET FOR CANCER THERAPY TARGETING WNT SIGNALING AND THE NHE-REGULATED CELLULAR PH

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In the last years growing evidence sustains the role of acidic tumor microenvironment in cancer cell proliferation, invasion and metastatization and in chemoresistance. Tumor cells are characterized by an alkaline intracellular pH (pH_i) and an acidic extracellular pH (pH_e), whose preservation is crucial for tumor progression and malignancy. This pH gradient is maintained by cancer cells through various pH regulators, such as Proton Pumps (PP) and Na^+/H^+ Exchangers (NHE) which have been found over-expressed on tumor cell surface. Numerous studies have also demonstrated the key role of deregulation or constitutive activation of the Wnt signaling pathway in the initiation and progression of different forms of human cancer. Hence, cellular pH regulators as well as molecular components in the Wnt pathway have been proposed as novel targets for cancer therapy. However, the existence of a cross-talk between the pH regulator activity and the canonical Wnt signaling has never been previously explored in tumor cells. Atrial Natriuretic Peptide (ANP) is a cardiac hormone playing a crucial role in cardiovascular homeostasis mainly through blood volume and pressure regulation. In the last years, the new property ascribed to ANP of inhibiting tumor growth both *in vitro* and *in vivo* has made this peptide an attractive candidate for anticancer therapy. The molecular mechanism underlying the anti-proliferative effect of ANP has been mainly related to its interaction with the specific receptors NPRs, through which this natriuretic hormone inhibits some metabolic targets critical for cancer development, including the Ras-MEK1⁄2-ERK1⁄2 kinase cascade, functioning as a multikinase inhibitor. In this study we demonstrated that the antitumor activity of this natriuretic hormone is also mediated by a concomitant effect on the Wnt/β-catenin pathway and on the NHE-1-regulated pH_i of cancer cells, through a Frizzled-related mechanism. Specifically, we showed that ANP triggered a NHE-1-mediated increase of the intracellular acidity, inhibiting the Wnt/ß-catenin signaling simultaneously. Conversely, we observed that the Wnt1a, a Wnt signaling activator, affected the intracellular pH in an opposite fashion. For the first time we obtained evidence for a cross-talk between the NHE-1 activity and the Wnt pathway in tumor cells. We suggested that Akt activity might be relevant in linking the NHE-1-regulated pH_i and the Wnt/β-catenin signaling. The peculiarity ascribed to ANP of simultaneously targeting two processes crucial for neoplastic transformation and solid tumor survival reinforces the utility of this natriuretic hormone for the development of both preventive and therapeutic strategies.

CAM IN THE TREATMENT OF CANCER RELATED SYMPTOMS: EPAAC PRELIMINARY DATA

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Background. Tuscan Region Health Department has the duty to review the international literature on the use of Complementary and Alternative Medicine (CAM) in oncology as Associated member in WP7 "Healthcare" of the *European Partnership for Action Against Cancer* (EU Commission, 2009).

Aims. The main purpose of its participation in the project is to review the scientific literature on the use, efficacy, safety, toxicity and drug interaction of CAM (acupuncture and traditional Chinese medicine-TCM, herbal medicine and homeopathy) in the integrative care of cancer-related symptoms and also produce "Guidelines" where acupuncture, herbal medicines and homeopathic drugs, used in cancer care and analyzed in RCTs are listed according to a standardized grading scale (SIO 2009).

Methods. Electronic and manual search through MEDLINE (databases: PubMed, Google Scholar and EBSCO) on CAM commonly used in human cancer treatment; the period was from January 2003 to June 2013. Systematic reviews, meta-analyses and RCTs in English were included and used the following MeSH terms: Cancer Symptoms (anemia, anxiety, depression, cancer related fatigue, constipation, diarrhea, edema and lymphedema, hot flashes, insomnia, mucositis, nausea, vomiting, neuropathy, neutropenia, pain, radiodermatitis, xerostomia) AND type of CAM (e.g. Herbal Medicine/Phytotheraphy, Homeopathy, Acupuncture and Traditional Chinese Medicine) AND Cancer or Oncology. Among the RCTs, randomized double-blind trials versus placebo were preferred and were chosen those trials that specify sample size, recruitment criteria and analysis methods, dosage and timing of natural compounds, tests and statistical power of the study.

Results. The work is in progress and its results will be presented in the Congress. However, so far a support for efficacy (grading SIO 2009 1A,1B,1C) was found for the following symptoms: nausea and vomiting, pain, hot flushes and xerostomia for acupuncture; anxiety and depression, cancer related fatigue, diarrhea, hot flushes, nausea and vomiting and pain for herbal medicine, and menopause related symptoms, mucositis, and radiodermatitis for homeopathy. For the other symptoms the evidence for the validity of CAM is limited.

Conclusion. The literature data on the use of CAM in cancer care has greatly increased during the last years. This is also due to the shift from an alternative pattern to the integrative vision of these disciplines. Complementary therapies may play an important role in the integrated treatment and control of symptoms associated with cancer and cancer treatment.

EFFICACY OF METFORMIN IN CANINE MAMMARY CARCINOMA: *IN VITRO* AND *IN VIVO* ACTIVITY ON CANCER STEM CELLS

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In recent years comparative oncology acquired a relevant role in cancer research highlighting the relevance of naturally developing cancers in animals as models for human disease and pharmacological research, although it is still an underutilized resource in translational oncology research. The present study focuses on spontaneous Canine Mammary Carcinoma (CMC) as experimental model for the study of anticancer activity of innovative drugs. The first step of our work was the isolation and characterization of Cancer Stem Cells (CSCs) derived from CMC post-surgical tissues. CSCs represent the tumorigenic cell subpopulation found within different human tumor types, able to generate tumors through the stem cell processes of self-renewal and chemo-and radio-resistance, causing relapse and metastasis. Therefore, development of specific therapies targeted to CSCs holds hope for improvement of treatment efficacy in cancer patients. In CMC-derived CSCs we evaluated the effects of metformin, a drug widely used in patients with type 2 diabetes, that has been associated with a lower cancer risk in epidemiologic studies. The stem phenotype of CSC cultures, has been investigated *in vitro* (by stem cell marker expression, self-renewal, proliferative potential) and *in vivo* (tumorigenicity in nude mice). Metformin is able to inhibit the proliferation of canine CMCs both *in vitro* and *in vivo* in xenograft tumors. On these bases a study on dogs bearing CMC treated with metformin before surgery has been planned. Preliminary results on 7 animals showed a significant block or decrease of tumor volume after metformin treatment. The ongoing research is aimed at increasing the number of dogs, to obtain reliable results that support the efficacy of metformin in targeting CSC of CMC, as potential neo-adjuvant agent in combination with current chemotherapeutic regimens and future translation into veterinary and human oncology.

NON-INVASIVE RADIO-FREQUENCY FOR EARLY DIAGNOSIS OF PROSTATE CANCER

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Since the early diagnosis has the potential to reduce mortality, it is important to involve new diagnostic tools for cancer investigation to prevent the unnecessary use of current diagnostic methods that are expensive, time-consuming, invasive, and uncomfortable. Early diagnosis for massive screening needs a medical device that is non-invasive (vs. DRE, colonscopy, mammography, prostate biopsy, rectal ultrasound, etc.), and with a higher Negative Predictive Value (NPV) than traditional diagnostic tests. Objective of this study was to evaluate the feasibility of prostate cancer detection using the ESO-MED 8G and to evaluate its diagnostic accuracy. ESO-MED 8G is an electromagnetic medical device that performs non-invasive diagnosis for the exclusion of neoplastic diseases. It is based on a transmitting probe that emits a low-power radiofrequency, a receiver equipment and a diagnostic software to evaluate the diagnostic parameters and to provide a clinician friendly graphical representation. 602 men (64±13 years) were evaluated with the ESO-MED 8G between November 2012 and September 2013 in a prostate unit. The patient normally dressed is placed standing in front of the receiver equipment while the probe is approached and moved over the anatomical area of interest. The presence of biochemical alterations in tissues changes the level of coupling between the transmitting probe and contact tissues returning a diagnostic indicator to discriminate tumor tissues. ESO-MED 8G sensitivity for the diagnosis of prostate cancer was 94.9%; specificity, positive and negative predictive values were 97.9, 88.1 and 99.1%; accuracy was 97.5%. Comparing the ESO-MED 8G with others diagnostic tests currently involved for prostate cancer investigation, the NPV (99.1%) is higher than PSA, DRE and rectal ultrasound, 72, 74 and 78% respectively. The results of this study confirm the possibility of electromagnetic exclusion of cancer. When the device response is negative it means that further invasive investigations are not necessary (NPV >99%). On the contrary when the response is positive it means that prostate biopsy or further investigations is recommended. Strengths of ESO-MED 8G are non-invasive and fast examination, use of non-ionizing radiation with very low intensity, and high-sensitivity (detection of tumor below 5 mm in size with high accuracy). In conclusion ESO-MED 8G represents the first-screening method that can be adopted to prevent unnecessary use of other uncomfortable diagnostic methods (e.g., DRE, rectal ultrasound for prostate).

THE ANTIPROLIFERATIVE EFFECTS OF CELLFOOD™ ON TUMOR CELL LINES

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Cellfood™ (CF) is a natural supplement containing 78 ionic/colloidal trace elements and minerals, 34 enzymes, and 17 amino acids, all suspended in a solution of deuterium sulphate (Everett Storey's formula). It has been evidenced that CF presents antioxidant activity *in vitro*, and that increases oxygen consumption and ATP mitochondrial production in endothelial cells. Aim of this study was to evaluate CF antiproliferative effects on tumor cell lines growing both in suspension (leukemia cells) and in adhesion (mesothelioma, melanoma, and colon, bladder, lung, and breast carcinoma). We observed that CF reduced cell proliferation by apoptosis induction. Indeed, in the leukemic cell lines Jurkat, U937, and K562, CF administration led to caspase-3 activation and nuclear DNA fragmentation, which are two biochemical markers of the apoptotic pathway. Apoptosis was related to reduced expression of the hypoxic factor HIF-1α and of the membrane glucose transporter GLUT-1. Energy metabolism modifications due to CF administration were also confirmed by the decreased activity of the glycolytic enzyme lactate dehydrogenase and by lower lactate levels in the extracellular medium. Studies on solid tumor cell lines also demonstrated that CF antiproliferative activity was due to apoptosis induction. In fact, cell cycle analysis in the mesothelioma cell line MSTO evidenced an increment of sub-G1 phase and a decrease of G1 phase after CF administration. The evaluation of pro-apoptotic protein expression confirmed the occurrence of cell death by apoptosis; indeed, caspase-3 activation, PARP cleavage, and p21 and p27 increment were observed in MSTO cells after CF treatment. In conclusion, we provide evidence that CF is able to inhibit tumor cell growth by altering cell metabolism and inducing apoptosis. Thanks to its antioxidant and pro-apoptotic properties, CF might be a good candidate for cancer prevention and may have clinical benefits in association with standard antineoplastic therapies.

HOMEOPATHY AND ACUPUNCTURE IN THE CLINICAL SETTING OF INTEGRATIVE MEDICINE FOR ONCOLOGICAL PATIENTS. THE EXPERIENCE OF THE CENTRE FOR INTEGRATIVE MEDICINE IN THE HOSPITAL OF PITIGLIANO (GR)

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Background. Cancer patients show a complex mixture of physical symptoms associated both to the cancer disease or its treatment (weariness, pain, nausea, anorexia, etc.) and to psychological stress (depression, anxiety) derived from the sickness. In order to manage all these concerns, integrative and complementary medicine has been introduced within various hospital or paramedical structures.

Aim. Tthe aim of the present contribution is giving an evaluation of the efficacy of integrative medicine on a sample of 140 oncological/cancer outpatients or inpatients within the centre of integrative medicine inside the hospital of Pitigliano (period: 2011-2012). The cure model adopted would be presented: in particular, the latter provided for a comprehensive protocol, comprising homeopathy, acupuncture and nutritional integration - diet advices given according to a therapeutic approach shaped on the single individual patient, as well as on the disease stage. The objectives of this method are the following: 1) supporting the adhesion to the conventional oncological therapy: 2) avoiding or limiting side-effects caused by chemo or radiotherapy; 3) improving and sustaining general conditions. Regarding the evaluation of the efficacy of the said "integrative" protocol, a follow-up has been set up, on the basis of the following elements: SF12, Edmonton scale mod., reduction of conventional drugs' consumption, especially those concerning the treatment of side-effects in chemo or radiotherapy, evaluation of the compliance to the oncological therapy. An anonymous survey has served the goal of measuring the level of satisfaction toward the received treatment.

Results. The results dealing with the said aims would be illustrated. In a nutshell - for what the sample of 140 oncological patients is concerned - it can be anticipated that the integrative therapy has determined a better compliance to the oncological cure (84%), an overall reduction of symptoms and a decrease in the usage of conventional drugs (75%).

TEA TREE OIL MIGHT AID COMBAT AGAINST MELANOMA

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Human melanoma is a highly invasive and metastatic tumor and, to date, is one of the most difficult cancers to fight with current treatments, due to its intrinsic resistance to chemotherapy and radiotherapy. Numerous experimental data and other clinical-pathological studies have shown that the drug-resistant phenotype is often associated with more aggressive behavior in tumors of different histological derivation. In particular, the overexpression of the xenobiotic transporter P-glycoprotein (P-gp) often correlates with a phenotype with a high invasive and metastatic potential. An our previous study showed that human melanoma cells (M14 WT) grown in the presence of adriamycin antitumoral drug (M14 ADR), expressed the multidrug transporter P-gp. This overexpression confered to M14 ADR cells cross resistance to adriamycin and vincristine, and increased resistance to caspase-dependent apoptosis (Fas-mediated, serum deprivation), when compared with M14 WT parental cells. In our lab we demonstrated that the essential oil steam (Tea Tree Oil, TTO) distilled from *Melaleuca alternifolia,* a species of northern New South Wales, Australia, was able to reverse the resistance of M14 ADR cells to the P-gp-mediated caspase-dependent apoptosis. TTO is an aboriginal Australian traditional medicine for bruises, insect bites, and skin infections. The effect of TTO on melanoma cells appeared to be mediated by its interaction with the lipid bilayer of the plasma membrane as delineated by a biophysical and ultrastructural study conducted by our group. In addition, as previously showed by our studies, the multidrug resistant M14 ADR cells displayed a more invasive phenotype compared to their parental counterparts M14 WT. This phenotype was accomplished by a different migration strategy adopted by resistant cells (‘chain collective’) already described in tumor cells with high metastatic capacity. Thus, the effect of TTO and of its main active component, terpinen-4-ol, on the migratory and invasive potential of M14 WT and M14 ADR cells was evaluated. To this aim, the transwell chamber invasion assay has been employed. The obtained results demonstrated that TTO and terpinen-4-ol, other than to overcome the resistance to apoptosis of MDR melanoma cells, are able to affect the aggressive behaviour of drug-resistant melanoma cells, by inhibiting the intracellular signaling stimulated by the MDR transporter. The lipophilic nature of the oil enables it to penetrate the skin, suggesting that it may be suitable for topical therapeutic use in the treatment of fungal mucosal and cutaneous diseases. This experimental evidence are suggestive of a new candidate to enlist in front line to fight against melanoma.

LIFE QUALITY: ESSENTIAL ITEM IN THE CASE OF BREAST DISEASE

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Dermo Digital Project, The First National Micropigmentation Academy has created a technical-clinical protocol for the treatment of post mastectomy mammary areolas that, through the use of three-dimensional graphic techniques of rigid patterns of light and dark, realizes natural and long lasting reconstruction treatments. The masking color on post-operative flat scars, is placed in a prominent position in the clinical activities, easily achievable through the use of DIGITAL PRO HAND, a last generation dermographer, able to develop over 4500 beats per minute by pulsing an anti-reflux more tips needle, which allows it to operate with a linear and fast covering stretch on the skin. Further fields of application are represented by both treatments of hypo and hyperchromic discoloration, such as melasma and vitiligo, and scalp thinning, scars and alopecia, obteining a natural shaved effect and a revitalizing stimulation of the hair bulb. The use of DDProject pigments can operate on any type of complexion, invisible in the tomographic results. The airless preserved, tested and certified by the most prestigious german testing laboratory pigments are present in more than 100 different shades of color. It is important to note that as a result of countless areola reconstruction surgeries or discolorations and scars tratments, cases of intolerance to inoculated pigments were never found. For some time the operating protocol for the micropigmentation is inserted in the post-operative phases of prestigious Italian University, specialized in plastic and oncology surgery, such as:

- la Fondazione Istituto Nazionale dei Tumori IRCCS di Milano;
- l'Istituto Nazionale dei tumori Regina Elena IRCCS IFO di Roma;
- la Fondazione Salvatore Maugeri Clinica del Lavoro e della Riabilitazione IRCCS di Pavia;
- l'ospedale G.B. Morgagni di Forlì;
- l'Istituto Nazionale per la Ricerca sul Cancro IST di Genova.

PSA

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The Prostate Specific Antigen (PSA) is an enzyme produced by the prostate. In serum PSA is present in small amounts and increases in pathological states such as prostatitis, prostatic hypertrophy (BPH) and prostate cancer do (CaP). The treatment of the gray zone, PSA between 4.0 ng/mL and 10.0 ng/mL, or with significant increase over time, and normal Digital Rectal Examination (DRE), can sometimes be a doubt as to whether or submit to drug immediately biopsy in the patient. In the past, since the studies of Lorente in 2002, the debate on the possibility that inflammatory processes influence prostate PSA and the methods to avoid unnecessary biopsies. The most common behavior is the administration of long-term antibiotic, 4-8 weeks, or a mix antibiotic - anti-inflammatory. Flying over the obvious considerations on the use and abuse of the antibiotic, purpose of the study is to verify the existence of an alternative method to the antibiotic, able to ensure the same effect without the side effects.

THE CELL MEMBRANE IS THE MAIN TARGET OF RESVERATROL AS SHOWN BY INTERDISCIPLINARY BIOMOLECULAR/CELLULAR AND BIOPHYSICAL APPROACHES

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Resveratrol (RV) is a poly-phenol non flavonoid compound belonging to the family of natural phytoalexins which are produced by plants to combat the attack of pathogens and/or stress. This molecule is particularly abundant in the berries of the red grapes (*Vitis vinifera*), but is also present in highly pigmented vegetables and fruit. This molecule shows a great number of biological activies, such as antitumor, antioxidant, phytoestrogen and antiviral. In our previous study we demostrated that RV inhibits the DNA replication of murine polyomavirus in a culture of mouse fibroblasts probably acting during the phase of viral penetration. In this work, the biological effects of the interaction of RV with the mouse fibroblast line 3T6 were investigated by bio-molecular/cellular and biophysical strategies. We evaluated the extent of cytoxicity, the kynetics of uptake and the effects on the cell cycle progression caused by RV. A non-invasive biophysical strategy, based on electrorotation was already used to study the membrane behavior of prokaryotic and eukaryotic cells subjected to chemical and biological stresses. With respect to this, electrorotation allows monitoring the alterations of the plasma membrane induced by a variety of external stimuli. Briefly, we studied the effects on cell vitality and cell cycle by MTT and cytofluorimetric assays. In addition we explored the action of resveratrol on the cell membrane by a well consolidated biophysical approach: electrorotation. This technique allows the assessment of the structure/function of the cell membrane. Our work suggested that RV may determine a damage of the plasma membrane The results demonstrated that resveratrol shows a modest effect on the biological properties of the cell in terms of cytoxicity and cell cycle alterations. On the contrary, a significant effect on the membrane structure/function was observed consisting in an enhanced intra-membrane ion transport. The implications and interpretation of these membrane alterations showed that the main target of resveratrol action is the cell membrane.

ACTIVE-SPECIFIC ANTI-CANCER IMMUNOTHERAPY WITH A POLY-PEPTIDE CONTAINING MULTIPLE CYTOTOXIC-T-LYMPHOCYTE EPITOPES OF THYMIDYLATE SYNTHASE

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TSPP is a 27-Mer Poly-Peptide containing three known CTL epitopes with HLA-A2.1 binding motifs of the Thymidylate Synthase (TS), an enzyme over-expressed in cancer cells and critical for their replication. We have tested the safety and the biological activity of TSPP vaccination in advanced cancer patients in a phase Ib trial. Twenty-one pre-treated/metastatic cancer patients with a good *performance status* (ECOG < 2), and no severe organ failure or immunological disease were enrolled in the study and administered with TSPP alone (arm-A) or in combination with GM-CSF and IL-2 (Arm B) in order to identify the Maximal-Tolerated-Dose (MTD) and the Most Effective-Biological-Dose (MEBD) of the vaccine. There was no grade 4 toxicity. The most common adverse events were grade 2-3 local dermatological reaction in the vaccine injection site, cough, rhinitis, fever, poly-arthralgia, gastro-enteric symptoms and to a lesser extent, hypertension and hypothyroidism. We detected a TS-specific CTL response, modulation in inflammatory markers and a general increase in auto-antibodies like ANA, ENA, cANCA and pANCA. MTD of TSPP vaccine was not achieved, while MEBD resulted in a range of 200-300 μg. We also recorded a partial response and six Stabilizations of Disease (SD) in the patients of arm A, and two SD those of arm B. Our results offer the rationale to evaluate the anti-tumor activity of TSPP alone in further trials.

NUTRITION AND CANCER: BEFORE, DURING AND AFTER CHEMO-RADIO-THERAPY

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Over the past twenty years we have seen a gradual change in medicine. From a simple cause/effect approach, a new integrative perspective is gradually coming, which links inextricably the patient, taken in his/her totality, to his/her disease and the environment where he/she lives. This undoubtedly occurs in cancer research and therapy, which is paving the way to new approaches and more effective intervention strategies, aimed not only at cellular target, for what concerns the mere struggle between good cells and bad cells, but at a definite attempt to influence the microenvironment where these cells live, proliferate and *die*. This is now possible by modulating nutrition, the simplest but more complex component of the environment we live (Nutritional Manipulation), as well as by using specific natural substances that, in defined dosages and methods of use, could play the role of Epigenetic Modulator (Nutraceuticals). The combined use of these two sciences (the Science of Nutrition and Nutraceuticals), in combination with the usual chemotherapy and radiotherapy protocols, is called Oncointegration. The ultimate aim of this new discipline is to make the extracellular matrices inhospitable and unsuitable to the neoplastic cell, by making their proliferation more difficult, by modifying the expression of the oncogenes directly involved in the pathogenesis or in the maintenance of the disease. In this way, it will be possible for the patient to face the cycle of chemotherapy with fewer side effects and carry it out without interruption for the entire planned course (Chemoprevention). The present work is born from a heterogeneous group of professionals in order to develop a quick reference tool, both for cancer patients and for all health operators. It is, indeed, essential to know which kind of foods and nutraceuticals have to be chosen, as well as the best recruitment methods, depending on the cancer type and the different treatment protocols.
The Protocol requires:

- 1st Step: Before Chemotherapy: Preparing the body to Chemotherapy;
- 2nd Step: Chemo's Day - Synergy with Empowerment;
- 3rd Step: After Chemo - nutrition with low growth factors (IGF and prolamins).

RESVERATROL-INDUCED AUTOPHAGY CONTRIBUTES TO THE INHIBITION OF EPSTEIN BARR VIRUS REPLICATION IN BURKITT'S LYMPHOMA CELLS

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We have previously examined the antiviral activity of resveratrol on the replication of Epstein Barr Virus (EBV), the etiologic agent of infectious mononucleosis and associated with several types of malignancies of epithelial and lymphoid origin. In a cellular context that allows *in vitro* EBV activation and lytic cycle progression through mechanisms closely resembling those that *in vivo* initiate and enable productive infection, we found that RV inhibited EBV lytic genes expression and the production of viral particles in a dose-dependent manner. We demonstrated that RV inhibited protein synthesis, decreased Reactive Oxygen Species (ROS) levels, and suppressed the EBV-induced activation of the redox-sensitive transcription factors NF-kB and AP-1. Autophagy is an intracellular process by which bulk cytoplasm is engulfed by double-membrane vesicles and shuttled to lysosomes for degradation. Microbial pathogens have evolved strategies to interfere, escape or even exploit the autophagic machinery. Because autophagy has been proposed as one of the main mechanisms altered by resveratrol, in these studies we wanted to assess whether the inhibition of EBV lytic cycle by resveratrol occurs via a modulation of the autophagic process. In Burkitt's derived Akata cells, the lytic cycle has been induced in the absence or in the presence of resveratrol and the autophagic process has been evaluated by detection of autophagic markers such as LC3II and Beclin-1. The results obtained show that the polyphenol inhibits EBV replication by activating the autophagic pathway in a dose- and time-dependent fashion. Undergoing studies are aimed to clarify at the molecular level, the relationship between resveratrol, autophagy and EBV lytic cycle.

POLYDATIN, A NATURAL PRECURSOR OF RESVERATROL, INDUCES CELL CYCLE ARREST AND DIFFERENTIATION OF HUMAN COLORECTAL CACO2 CELL

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Human colon adenocarcinoma cells are resistant to chemotherapeutic agents, such as anthracyclines, that induce death by increasing the reactive oxygen species. A number of studies have been focused on chemo-preventive use of resveratrol as antioxidant against cardiovascular diseases, aging and cancer. While resveratrol cytotoxic action was due to its pro-oxidant properties. In this study, we investigate whether the Resveratrol (trans-3,5,49-trihydroxystilbene) and its natural precursor Polydatin (resveratrol-3-O-b-mono- D-glucoside, the glycoside form of resveratrol) combination, might have a cooperative antitumor effect on either growing or differentiated human adenocarcinoma colon cancer cells. The polydatin and resveratrol pharmacological interaction was evaluated *in vitro* on growing and differentiated Caco-2 cell lines by median drug effect analysis calculating a combination index with CalcuSyn software. We have selected a synergistic combination and we have evaluated its effect on the biological and molecular mechanisms of cell death. Simultaneous exposure to polydatin and resveratrol produced synergistic antiproliferative effects compared with single compound treatment. We demonstrated that polydatin alone or in combination with resveratrol at 3:1 molar ratio synergistically modulated oxidative stress, cell cycle, differentiation and apoptosis. Worthy of note treatment with polydatin induced a nuclear localization and decreased expression of heat shock protein 27, and vimentin redistributed within the cell. From morphological, and biochemical outcome we obtained evidences that polydatin induced a transition from a proliferative morphology to cell-specific differentiated structures and caused human CaCo-2 cell death by induction of apoptosis. Our data suggest the potential use of polydatin in combination chemotherapy for human colon cancer.

BIOLOGICAL EFFECTS IN GLIOBLASTOMA STEM CELLS AFTER CHARGE-PARTICLE IRRADIATION: HADRONTHERAPY AS A NEW THERAPEUTIC OPPORTUNITY?

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Glioblastoma Multiforme (GMB) is the most common type of malignant primary brain tumor in adults. Despite the treatments with established therapies as surgery, radiation therapy and concomitant adjuvant chemotherapy with temozolomide, the median survival is still in the range of just 12 months. The high recurrence rate and failure of conventional treatments can be explained by a recent cancer model that assumes the presence of stem cells inside the tumour mass having a greater resistance to standard therapeutic approaches. In this context, there is much interest in elucidating the mechanisms of resistance to radiation therapy and developing novel, more effective approaches. Some literature data report that Glioma Stem Cells (GSCs) promote radioresistance to gamma rays by preferential activation of the DNA damage response followed by a better capability to repair DNA damage. Moreover, recent experimental evidence showed a higher effectiveness of carbon ions respect to photons in inactivating cancer stem cells from colon carcinoma, likely related to the different quality of the induced DNA damage. These results suggest a potential advantage of Hadrontherapy (that use external beams of charged particles) compared with conventional radiotherapy. Clinical trials already started at the Hidelberg Ion-beam Therapy Center (HIT) with promising results. In order to investigate the mechanisms involved in the molecular and cellular response of GSC to ionizing radiations, we irradiated two GSC lines (namely #1 and #83), derived from patients with different clinical outcome, with 137Cs photons at the Istituto Superiore di Sanità, Rome, and with protons or carbon ions with energy of about 62 MeV/u at the Laboratori Nazionali del Sud LNS-INFN, Catania. The dose range was 1-40 Gy. The biological effects investigated have been DNA damage and repair, cell cycle progression and cell death as measured by flow cytometer and clonogenic survival assay, respectively. The results so far obtained show some differences in the radiation response depending on the cell line and radiation type. In particular, when compared to photons, charged particles, especially C-

ions, seem to be more effective in inactivating GSCs, as pointed out by the clonogenic analysis. This can be related to the different quality of the induced DNA damage, highlighting a potential advantage of Hadrontherapy in glioblastoma patients. Further experiments are in progress to consolidate data and to get more insights on the relationship among the different end points investigated at molecular and cellular level. This work was partly supported by INFN ("RADIOSTEM" Project).

LIPOSOMAL IRON IS BETTER THAN IRON SULFATE IN LOW-RISK MYELODYSPLASTIC SYNDROMES (LR-MDS) WITH MILD ANEMIA. MONOCERNTRIC STUDY

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Background. LR-MDS frequently shows a chronic inflammatory status, ferritin high values and impaired capacity of iron absorption and utilization. Liposome has a described anti-inflammatory effect and transports its content directly in blood, beyond gastric and enteric wall.

Aim. Aim of this study is to verify if liposomal iron support in Refractory Anemia (RA) and refractory Cytopenia with Multilineage Dysplasia (RCMD) with mild anemia is safe and effective in increasing hemoglobin level.

Patients and methods. In group A 7 patients (5RCMD and 2RA), with normal cytogenetics, M/F:4/3, median age 65 years (R64-75), Hb 10.7 g/dl (R10-11.5), saturation of iron binding capacity >20%, with a median ferritin level of 480 ng/ml (R380-550), ESR 28 mm/1st hour (R20-32), CRP 6 mg/I (R4-7), normal B12 and folate, received liposomal iron 30 mg/day orally for 3 months. In group B 7 patients (3RCMD and 4RA), with normal cytogenetics, M/F:5/2, median age 63 years (R62-70), Hb 11 g/dl (R10.8-12), saturation of iron binding capacity >20%, with a median ferritin level of 430 ng/ml (R370-580), median ESR 30 mm/1st hour (R18-38), median CRP 7 mg/I (R5-7), normal B12 and folate, received support with iron sulfate 105 mg orally/day.

Results. Group A showed a median hemoglobin increase of 1.5 g/dl (R0-2), a ferritin decrease to a median of 160 ng/ml (R 100-250), a ESR decrease to a median value of 15 mm/1st hour (R 8-20) and a median CRP 3 mg/I (R2-5). In group B no significative increase of hemoglobin or decrease of ferritin, ESR and CRP were recorded. 2 patients showed hepygastralgia, 2 stipsis, 2 diarrohea.

Conclusion. Liposomial iron is safe, effective, well tolerated, effective in increase hemoglobin level and reduce inflammatory markers in low-risk MDS.

LIPOSOMIAL IRON HAS AN ANTI-INFLAMMATORY EFFECT AND IS BETTER THAN IRON SULFATE IN CORRECTION OF ANEMIA OF CHRONIC INFLAMMATORY DISEASE OF YOUNG WOMEN

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Background. Liposome has a described anti-inflammatory effect and transports its content directly in blood, beyond gastric and enteric wall.

Aim. Aim of this study is to verify if liposomial iron is most effective than iron sulfate in correction of anemia of chronic inflammatory disease of young women.

Patients and methods. In group A 9 patients (4 with systemic erythematous lupus, 3 with mixed connectivitis, 2 with rheumatic fibromyalgia), median age 32 years (R27-42), Hb 8.5 g/dl (R8-10), saturation of iron binding capacity < 20%, with a median ferritin level of 100 ng/ml (R90-250), ESR 35 mm/1st hour (R22-95), CRP 18 mg/I (R12-24), normal B12 and folate, received liposomal iron 60 mg/day orally for 3 months. In group B 12 patients (6 with systemic erythematous lupus, 3 with mixed connectivitis, 3 with rheumatic fibromyalgia), median age 38 years (R29-45), Hb 9 g/dl (R8-9.5), saturation of iron binding capacity < 20%, with a median ferritin level of 120 ng/ml (R80-190), ESR 33 mm/1st hour (R20-87), CRP 15 mg/I (R13-27), normal B12 and folate, received iron sulfate 210 mg/day orally for 3 months.

Results. After treatment, group A showed a median hemoglobin level of 11.5 g/dl (R10.5-12), a median ferritin level of 260 ng/ml (R 190-280), a ESR decrease to a median value of 8 mm/1st hour (R 3-10) and a median CRP 3 mg/I (R2-4). After treatment, group B showed a median hemoglobin level of 9.5 g/dl (R8-9.5), a median ferritin level of 100 ng/ml (R 90-180), and ESR and CRP don't showed any improvement. 4 patients showed hepygastralgia, 2 stipsis, 5 diarrohea.

Conclusion. Liposomial iron is most safe, effective, well tolerated, effective than iron sulfate in increase hemoglobin level and reduce inflammatory markers in correction of anemia of chronic inflammatory disease of young women.

MELATHONIN PLUS DANAZOLE, PREDNISONE AND ERYTHROPOIETIN ALPHA IS EFFECTIVE IN TREATMENT OF MYELODYSPLASTIC SYNDROMES WITH ANEMIA AND THROMBOCYTOPENIA

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Background. Melathonin was reported effective in some cases of ITP because of its thrombopoietic effect.

Aim. Aim of this study is to verify if danazole, prednisone, melathonin and erythropoietin alpha is effective and safe in patients with Refractory Cytopenia With Multilineage Dysplasia (RCMD) with anemia and thrombocytopenia.

Patients and methods. This study is a multicentric study. 20 patients with RCMD with IPSS intermediate or low showed anemia and thrombocytopenia. Cytogenetics was normal in 15 patients and not evaluable in 5 patients. In group A 10 patients received orally danazole 200 mg/day, prednisone 25 mg/day, melathonin 60 mg/day, B12 400 mg/day, calcium levofolinate 7.5 mg/day, liposomal iron 30 mg/day, erythropoietin alpha 40000 IU subcutaneous weekly (5 originator and 5 biosimilar) for at least 3 months. In group B 10 patients received the same treatment except melathonin. In group B 7 patients received originator erythropoietin alpha and 3 biosimilar. In group A M/F was 6/4, median age was 68 years (R62-80), median follow-up was 4 months (R2-6), median Hb 9 g/dl (R8.5-10), median PLT count 40000/mcl (R30000-50000). In group B M/F was 5/5, median age was 66 years (R60-84), median follow-up was 3 months (R2-5), median Hb 8.7 g/dl (R8-9.5), median PLT count 27000/mcl (R20000-45000).

Results. In group A median platelet count after treatment was 55000/mcl (R40000-60000), median Hb 10 g/dl (R9-11). In group B median platelet count after treatment was 38000/mcl (R25000-50000), median Hb 10.2 g/dl (R9-10.5). In group A the 5 patients receiving biosimilar erythropoietin alpha showed a median platelet count of 55000/mcl vs a median platelet count of 40000/mcl in patients receiving originator molecule. No side effects were noted in the two group.

Conclusion. Melathonin, danazole, prednisone and erythropoietin alpha is safe and effective in RCMD with anemia and thrombocytopenia.

METRONOMIC THERAPHY IN VERY OLD PATIENTS: WHEN TO TREAT AT HOME BED IT'S NOT SO BAD

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Aim. Aim of this study is to verify if metronomic therapy, already used in solid tumours, is not inferior and less toxic than standard chemotherapy in treatment of aggressive lymphomas of very old patients.

Patients and methods. We considered 26 patients from 2009 to 2013. To calculate frailty of patients CHARLSON, CIRS-G, CRASH and GISL score were used. In group A patients were treated at home with metronomic therapy with cyclophosfamide 50 mg days 1to5, etoposide 50 mg days1-3-5, prednisone 25 mg days 1to7, lenalidomide 10 mg days 1to21, all orally, every 28 days for 9-12 cycles (Large B Cell Lymphoma and Mantle Cell Lymphoma), or with cyclophosphamide 50 mg days 1to3, fludarabine 25 mg days 1to3, etoposide days 4to6, prednisone 25 mg days 1to15, all orally, methotrexate 15 mg im day15, every 28 days for 9-12 cycles (T cell Lymphoma). In group B patients received at hospital i.v. Rituximab 375 mg/sqm day1, Cyclophosphamide 750 mg/sqm day1, adryamicin 50 mg/sqm day1, prednisone 50 mg/sqm orally day 1to5 (Large B Cell Lymphoma, T cell lymphoma and Mantle Cell Lymphoma). In group A M/F:8/8, median age was 85.5 years (R85-94), TNHL/DLBCL/MCL:5/4/1, median IPI 4(R2-5), median follow-up was 6 months(R2-13), 9 patients showed 1 comorbidity (56%), 7 patients 2 or more (44%); CHARLSON>5:12pat(75%), CIRS-G=4:9pat.(56%), CRASH>9:7pat(43%), GISL FRAIL:12pat.(75%). In group B M/F:4/6, median age was 85 years (R85-91), TNHL/DLBCL:2/8, median IPI 4(R2-5), median follow-up was 6 months(R1-24), 2 patients showed 1 comorbidity (20%), 2 patients 2 or more (20%), 6 patients no comorbidities (60%) CHARLSON>5:4pat(40%), CIRS-G=4:5pat.(50%), CRASH>9:3pat(30%), GISL FRAIL:5pat.(50%). SF8 questionnaire was used to evaluate quality of life of patients.

Results. In group A median hospitalization was 0 weeks (R0-12), complete remission 4 patients (25%), partial remission 8 patients (50%), progression of disease 4 patients (25%), G3/G4 toxicities (hematologic 25%, not hematologic 25%, infection 37%, transfusion 19%, death 37.5%), days of hospitalization/days of global survival 5%(R0-25), cost per month of survival € 5,000 (R250-9100), SF8 60 (R40-100). In group B median hospitalization was 9 weeks (R3-17), complete remission 5 patients (50%), partial remission 2 patients (20%), progression of disease 3 patients (30%), G3/G4 toxicities (hematologic 70%, not hematologic 50%, infection 40%, transfusion 80%, death 60%), days of hospitalization/days of global survival 33%(R20-100), cost per month of survival € 21000 (R5000-37000), SF8 40 (R20-50). At Kaplan-Mayer analysis median survival was 18 months for both groups.

Conclusion. Metronomic therapy is cost-effective and warrants a good quality of life and survival in very old patients.

SUPPORT TREATMENT IN CANCER PATIENTS: RESULTS OF TWO SELF-EVALUATION TEST

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The extension of the average lifespan, unhealthy lifestyles, an environment pollution, nutrition habits that pay little attention to quality, the spread of early diagnosis are among the main causes of the absolute incidence of cancer cases that doctors and society must face. The patient suddenly finds himself in a world where extreme technological medical approach and the depersonalization, of which often suffers, feeling like a victim, along with the profound physical and psychological discomfort, led him to seek help in the variegated world of non-conventional medicine. In addition, the approach mainly based on the "cancellation" of the cancer from the body of the patient, is experienced as a lack of attention to its global needs. The lack of knowledge and distrust of some oncologists toward supportive care cause that the patient very frequently does not communicate to physicians that are using CAM methods. The result is that often, after a search on the internet and in the inability to discern what makes sense from what has none, is subjected to unnecessary therapy, or who may decrease the effectiveness of chemotherapy. Moreover patient is subtracted from well studied CAM therapies, possessing positive clinical and experimental indications: there is no shortage of publications and observations. Here is demonstrated, by clinical observations, how some supports can be safely used, and with excellent results, in improving the health status of the cancer patient in chemo/radiation treatment. In patients receiving chemotherapy/radiotherapy were administered two patented questionnaires, commonly used for the objective quantification of the level of perceived well-being, which have been compiled at regular intervals for a year. The results show a steady and progressive improvement of all parameters considered. Together with laboratory parameters and imaging these results have been peer-reviewed and accepted for publication.

VISCUM ALBUM FERMENTATUM PINI VERSUS ORAL ETOPOSIDE AS ADJUVANT TREATMENT IN OSTEOSARCOMA PATIENTS AFTER SECOND RELAPSE

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Background. Osteosarcoma is a highly malignant bone tumor. With neoadjuvant chemotherapy it can be cured in approximately 60-70% of cases. Few drugs are currently available for relapsed and inoperable patients. We know from historical controls that the risk to relapse increases after the second relapse. Post Relapse Free Survival (PRFS) is < 20% after 12 months. Oral Etoposide is often used in clinical practice. Interferon (IFN) and Mifamurtide (L-MTP-PE, "Mepact") have been tried as adjuvant treatment in osteosarcoma with encouraging results (improved OS 7%).

Methods and materials. Viscum Album fermentatum Pini (VA-P) is a highly popular herbal medicinal product across central Europe with immunomodulatory activity. Encouraged by the preliminary findings of a pilot study that showed a prolonged Disease-Free Survival (DFS) of more than 12 months in four of five osteosarcoma treated with VA-P patients after their second relapse, we started a two-arm randomized study with VA-P s.c. and oral Etoposide in patients with histologically confirmed diagnosis of osteosarcoma or spindle cell sarcoma of the bone free from disease after their second metastatic relapse. Primary end point was the PRDFS rate at 12 months compared separately for each treatment arm to an expected rate of 12% derived from an historical group of patients.

Results. The study had to be terminated early due to slow recruitment. The planned interim analysis with 20 of the total 36 patients was redefined as final analysis, with 9 vs. 11 patients in the VA-P vs. Etoposide arm, 44% vs. 64% males, and mean age of 28 vs. 39 years (range 11-66), respectively. Median follow-up duration actually is 38.5 months (range 3-73), with follow-up times of 56 (24-73) months for VA-P and 25 (3-62) months for Etoposide. Median PRDFS in the Etoposide arm was 7 months while PRDFS probability in the VA-P arm did not fall below 55% even after more than five years since start of the study. PRDFS rates after 12 months for the VA-P and Etoposide arm were 55.6% (95% CI: 21.2%-86.3%) and 27.2% (6.0%-61.0%), respectively. VA-P was well tolerated, showing a remarkably better safety profile than Etoposide.

Conclusion. Viscum album fermentatum Pini (VA-P) shows promise as adjuvant treatment in prolonging DFS after a second relapse. First data indicate a similar advantage compared to other immunostimulants (IFN, L-MTP-PE), yet at a lower cost. A larger multi-center trial is required to determine efficacy of VA-P therapy in osteosarcoma patients compared to other immunostimulants currently approved in osteosarcoma treatment like L-MTP-PE.

POTENTIAL PHARMACOLOGICAL BIOACTIVE COMPOUNDS FROM ELICITATED STRAWBERRY *IN VITRO* CULTURES

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The growth of *in vitro* plants under controlled conditions allows obtaining useful and continue quantities of secondary metabolites. The aim of our study is to optimize the production of phenolics from *in vitro* cultures of plant cells or tissues, using the technique of micropropagation, and to evaluate the anticancer effects of these substances. The standardization of protocols for plant growing *in vitro* (cell suspensions, callus cultures and seedlings) is made by modulating the physical and chemical *in vitro* culture conditions (quality of light and or plant growth regulators) of vegetative tissues. Strawberry contains phenolic compounds that have antioxidant and anticancer properties. The first experimental phase included the induction of callus formation from leaf explants of *in vitro* growing shoots of strawberry (*Fragaria x ananassa* Duch, cv Don.), from the germoplasm collection of the CRA-Centro di Ricerca per la Frutticoltura di Roma, inoculated on medium containing appropriate nutrients and growth regulator concentrations. After a growth period of 30 days, calli were transferred to liquid medium for obtaining cell suspension cultures. Cell suspensions were treated by changing spectra light: blue (400-600 nm, maximum at 450 nm), red (675 nm) and standard light. Photoperiod was of 16 hours; the treatments lasted 8 days. The second experimental phase involved optimization of phenolics extraction and partial purification from cell suspension cultures. In the third phase normal (fibroblast) and transformed cell lines (Caco-2 and Ht-29) were treated with different amounts of extracts with the aim of evaluating the anticancer effect of these substances in term of antiproliferative effects. When normal fibroblasts were exposed to the phenolics from strawberry cell suspensions obtained under growth with the three lights (4,5 ug/ml, HPLC quantitation) no differences in cell number were obtained. By contrast, when applied to transformed cells the three lights provoked different responses, the red light being the most powerful in inducing an antiproliferative effect. Our preliminary results, concerning the antiproliferative activity of extracts on Caco-2 and Ht-29 cells, underline the potential of these berry cultures for the production of pharmacological bioactive compounds. Since changes of biological activity of phenolics extracted from such elicited plant cells may be due to variations in their composition, works are in progress to characterise single compounds of the extracts produced by cell suspension cultivated with red and blue light as elicitors.

COMBINED SYNERGY BETWEEN TYPE I IFN AND 5-AZA-2'-DEOXYCITIDINE IN THE INHIBITION OF SOLID CANCER PROGRESSION

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Type I Interferons (IFN-I) are a family of cytokines that exert anti-tumor activities through both direct tumor cell growth inhibition and stimulation of host immune responses, gaining wide applicability in clinical oncology. However, resistance to IFN-I-induced antiproliferative and pro-apoptotic effects has been reported in many hematologic and solid malignancies. Molecular studies have postulated that such resistance results from epigenetic silencing by DNA methylation of IFN-stimulated genes that limit IFN-I responsiveness in cancer cells. 5-Aza-2'-Deoxycitidine (Aza) is an anti-methylating drug that effectively reactivates epigenetically silenced tumor suppressor genes *in vitro* and *in vivo*, suggesting that epigenetic re-activation of silenced IFN-stimulated genes in cancer cells by Aza treatment may be exploited to enhance the susceptibility to IFN-I-induced antiproliferative and apoptotic effects. In this study, we evidenced that a combined administration of IFN-I and Aza significantly inhibits the growth of murine and human melanoma and colon cancer cells. We show that tumor cells treated with IFN-I plus Aza exhibit a higher apoptotic rate and undergo cell cycle arrest, with respect to control cells and to cells exposed to single treatments. When transplanted into recipient mice, IFN/Aza-treated B16-F10 metastatic murine melanoma cells display a drastic delay in tumor progression indicating a loss of tumorigenic potential, with respect to controls. Overall, our findings suggest that a combined synergy between Aza and IFN may be essential for a more effective inhibition of tumor growth and provide more insights on the possible application of multidrug therapies for management of cancer patients.

MAGNOLIA'S ROLE IN BIONATURAL CANCER THERAPY

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Several experimental studies have demonstrated the existence in nature of many herbs or plants equipped with anti-tumor action, on the basis of well-defined biochemical mechanisms. These include the active ingredients of Magnolia seem to be the ones who more than any other can come to affect the malignant progression. It has been demonstrated that the honokiol, the main active principle of Magnolia is able to selectively inhibit the activation of some protein kinases involved directly in the process of neoplastic transformation. The purpose of this phase II study was to evaluate the effect on 1-year survival for the addition of Magnolia in the treatment of incurable cancer patients than observed in the past with the scheme including MLT, Aloe arborescens and myrrh. The study was conducted on 14 patients (M/F: 5/9, median age 56 years, range 52-74, median ECOG PS: 1, range 0-2) with locally advanced or metastatic solid tumor and not likely to standard medical therapies, with life expectancy of less than 1 year. Histotypes neoplasia are the following: adenocarcinoma of the pancreas: 4; pulmonary adenocarcinoma: 3; colon adenocarcinoma: 2; adenocarcinoma of the stomach: 1; endometrial adenocarcinoma: 1; ovarian carcinoma: 1; sarcoma: 1; glioblastoma: 1. Distant metastases are present in 13/14 patients and the seats dominant are the following: lung: 6; liver: 3; lung + liver: 1; peritoneum: 2; brain: 1. Compared with the previous scheme with MLT, Aloe arborescens and Myrrh, the Magnolia bark has been used. Were prepared tablets of 500 mg and the dose was to 500 mg x 2/day every day without interruption until progression. The radiological controls were performed before treatment and at intervals of 3 months. The clinical response was assessed by WHO criteria. Statistical analysis was performed using the chi-square test. Were observed 2 Partial Responses (PR) of the 14 patients (14%), 8/14 patients (57%) reported Stable Disease (SD), Disease Control (DC) in 10/14 (71%), while the remaining 4 patients had a rapid Disease Progression (PD). Higher survival at 1 year was achieved in 7/14 (50%) patients. Although the results of this preliminary study phase II will have to be confirmed by controlled clinical trials of appropriate case studies, the data appear to be already sufficient evidence to suggest that the addition of Magnolia is essential in the treatment of cancer bio-natural compared to the previous treatment with MLT, aloe and myrrh.

A NEW THERAPEUTIC APPROACH USING THE COMBINED TREATMENT OF CHLOROQUINE WITH ENZYMATIC SPERMINE METABOLITES

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In the development of new treatments against tumours the differences between normal and cancer cells must be considered. One of such differences is concerned with the polyamine content and metabolism. The content of polyamines, such as putrescine, Spermidine and Spermine (Spm), is increased in tumour cells in comparison with their normal counterparts. Increased polyamine levels are associated with increased cell proliferation, decreased apoptosis and down-expression of genes affecting tumour invasion and metastasis. Moreover, the natural polyamines are also source of cytotoxic metabolites, because they are substrates of a large class of enzymes, named amine oxidases. Our previous studies demonstrated that these enzymes catalyze the oxidative deamination of polyamines to generate cytotoxic products, H2O2 and aldehydes, that induce apoptotic and non apoptotic cell death. Such products also proved to induce a higher cell death on MDR melanoma cells than on the corresponding wild-type cells. It was demonstrated that the combination of BSAO/Spm with either docetaxel or interferon alpha had a synergistic effect on the inhibition of cell growth through apoptosis in both human epidermoid KB and breast cancer MCF-7 cell lines. Noticeably, our previous studies demonstrated that the induction of cell death, in colon adenocarcinoma (LoVo) and melanoma (M14) cancer cells, was potentiated by the combined treatments of BSAO/Spm with MDL72527 [N1,N4-bis(2,3-butadienyl)-1,4-butanediamine dihydrochloride], an inactivator of flavin-adenin-dinucleotide (FAD)-dependent Amine Oxidase (AO) with lysosomotropic properties. Thus, the aim of this study was to verify if also Chloroquine (CQ), 4-aminoquinoline, a well known lysosomotropic compound, was able to sensitize tumour cells to the cytotoxic activity of spermine metabolites. CQ is a drug widely used for the therapy of malaria, and as an anti-inflammatory agent for the treatment of several diseases, like rheumatoid arthritis, lupus erythematosus and amoebic hepatitis, by targeting the polyamine pathway. Thus, a systematic exploration of this group of compounds in cancer therapy seems of interest. Recently, CQ has been studied as an enhancing agent in cancer therapy. In the present study the effect of pre-treatment with CQ, on the cytotoxicity of the spermine metabolites, was evaluated on wild-type human melanoma cells (M14 WT) and the corresponding doxorubicin-induced MDR cells (M14 ADR2).

INTEGRATIVE APPROACH TO THE CANCER CARE: TUMOR METASTATIS TREATMENT

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A multimodal approach to oncological pathology allows you to attack the neoplastic cells from various angles and parallel support the healthy part of the body in the fight against the disease. In particular appears valuable support of immunity which physiological defense against aberrant cells and balance disorders in the body. From this point of view oncological hyperthermia is a part of an integrated path and must be used as direct proapoptotic agent, synergistically with other cancer therapies (chemotherapy and/or radiotherapy platin), immunomodulating, and liberating analgesic endorphins. I will present three clinical cases with a comprehensive approach to cancer problem. In the specific, case of a patient affected by leiomyosarcoma in diffusive phase, a patient suffering from metastatic breast cancer and a patient suffering from cerebral lymphoma; all in good disease control.

P1932, A NATURAL CELL PENETRATING PEPTIDE FROM SALIVARY BASIC PROLINE RICH PROTEINS

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Small human salivary peptides account for almost 2,000 molecules most of which derive from the post-translational and post-secretory processing of the acidic and basic proline-rich proteins. This plethora of peptides ranging from 1,000 to 6,000 Da still represents a mystery relating to their biological role. One of these, p1932, a 19 residues peptide (sequence: NH_2-GPPPQGGNKPQGPPPPGKPQ), is commonly found in human saliva. Due to its structural characteristics, one of the features we wanted to focus in this study was its ability to be internalized within cells of oral mucosa. The natural peptide and its retro-inverso-D forms were studied in a primary human gingival fibroblasts cell line and in a squamous tongue cancer cell line. We demonstrated by mass spectrometry, flow cytometry and laser scanning confocal microscopy that both peptide forms were able to enter cells on a time scale of minutes, being the L-form more kinetically efficient than the D-form. The cell uptake kinetic seem dependent on the cell cycle; peptide internalization is in fact more rapid in non-synchronized than in synchronized cells. Both peptides were readily internalized by a lipid raft-mediated endocytosis mechanism as confirmed by the reduced uptake at lower temperature and in the presence of methyl-β-cyclodextrin. These results suggest that p1932 may exert its biological role after internalization within the cells of oral mucosa. Furthermore, lack of any cytotoxicity of both peptide forms highlights their possible application as potential drug delivery agents.

NEXT-GENERATION HISTOPATHOLOGIC DIAGNOSIS: A LESSON FROM A RARE TUMOR

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Background. Hepatic carcinosarcoma is a deadly neoplasia characterized by the mixture of carcinomatous and sarcomatous elements. Its rarity and biphasic nature render histogenetic classifications unsure and therapeutic approaches subjective.

Patient and methods. The diverse histologic components of a hepatic carcinosarcoma were microdissected and subjected to simultaneous sequencing of 46 cancerassociated genes using Ion Torrent PGM™.

Results. The carcinosarcoma had a hepatocarcinoma and a sarcomatous component showing areas of rhabdomyosarcomatous differentiation. An intra-hepatic satellite hepatocarcinoma was also present. The primary and satellite hepatocarcinomas and both sarcomatous components disclosed the same TP53 mutation (F109C). The primary and satellite hepatocarcinomas had different PIK3CA mutations, H1047R and E545D, respectively; the satellite hepatocarcinoma also had two FGFR2 (C383R and M391T) mutations. The sarcoma showed two distinct FGFR3 mutations, S400fs in the poorly differentiated and G405fs in the rabhdomyosarcoma portion. A germline VEGFR2 variant (Q472H) was also found.

Conclusions. The case presented is an example of a "next generation histopathological diagnosis". Our morphology-driven geographical mutational analysis of 46 genes using routinely processed formalin-fixed paraffin-embedded tissues: i) supports the monoclonal origin of carcinosarcoma, as all the components shared the same TP53 mutation; ii) is able to trace the clonal evolution of the neoplasm, thus permitting the description of cancer heterogeneity in a diagnostic report; and iii) identifies potential therapeutical targets, where agents currently in clinical trials for different tumor types, such as those blocking PIK3CA, FGFRs and VEGFR2 mutated gene products, could be of use.

IS ANY IMPACT OF AHCC ON THE IMMUNOLOGICAL SYSTEM IN PATIENTS WITH NEUROENDOCRINE TUMORS (NETS) AFTER TREATMENT WITH THE RADIOISOTOPE PREPARATION (^{90}Y-DOTA-TATE)? - AN INITIAL REPORT

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Active Hexose Correlated Compound (AHCC) is an alpha-glucan rich "nutritional supplement" produced from the *mycelia* of shiitake (*Lentinula edodes*) of the basidiomycete family of "mushrooms". Human clinical studies have shown that AHCC significantly improves immune response, increases and maintains normal NK cell activity, and enhances macrophage and T-Cell activity.

The aim of the study. Assessment of the efficacy of AHCC in NETs patients on the immunological system three months after the last dose of 90Y-DOTA-TATE. The main purpose of our study in the future will be the evaluation of the influence of AHCC on immunological profile, TTP (Time To Progression), PFS (Progression-Free Survival), OS (Overall Survival) and RR (Response Rate).

Material and methods. We evaluated three patients with histopatological confirmed NETs, which were included in the study. These patients were treated with four doses of 90Y-DOTA-TATE (3.7 GBq/m2/dose) in 8-10 week intervals. Control CT and PET/CT with somatostatin analog 68Ga-DOTA-TATE were conducted three months after the last dose of 90Y-DOTA-TATE. Patients took AHCC doses in the amount of 6 g daily (3 x 2 g), 40 minutes before meals. The local ethics committee approval was obtained before the study commenced.

Results. All results are presented as medium results. Three months after the last dose of 90Y-DOTA-TATE the following was found: CD3+CD8+ and CD3-CD16/56+ cells increased by 60.43% and 18.84% respectively CD3+, CD3+CD4+, CD3+CD16/56+ and CD4+CD25++FoxP3+ cells decreased by 4.91%, 36.27%, 14.48% and 28.2% respectively. In PET/CT and CT, partial responses were revealed after this combined therapy (90Y-DOTA-TATE + AHCC).

Conclusions. AHCC is a promising extract, which increases the amount of CD3+CD8+ and CD3-CD16/56+ cells and decreases CD4+CD25++FoxP3+ in patients with NETs. In the further study we want to find out if decrease CD3+, CD3+CD4+, CD3+CD16/56+ cell are important for NETs patients and check whether these results will be confirmed in others patients.

ANTIMICROBICAL ACTIVITY OF ESSENTIAL OILS

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Use of herbal medicine in the world represents a long history of human interactions with the environment. Plants used for traditional medicine contain a wild range of substances that can be used to treat different infectious diseases. Essential oils are one of the most promising groups of natural compounds for the development of novel antimicrobial agents and they have been known to have antimicrobial activities, since antiquity. Essential oils possess a broad spectrum of antimicrobial activity, are is certainly related to the high content of terpenes and terpinoides. Essential oil are complex mixtures of several organic substances, in different quantities, only two or three main components, which are present in high concentration, are responsible to biological activity. The widespread use of antimicrobial drugs, contribute to the spread of resistance. This problem of increasing resistance has necessitated the search for safe and effective factors that may be used to treat persistent infections. In light of this, the antimicrobial activity of different essential oils as *Thymus vulgaris*, *Geranium*, *Cuminum cyminum L.*, *Ocimum basilicum*, *Citrus × aurantium L.* (citronel), *Cymbopogon nardus*, *Cymbopogon martini* (palmarose), *Carvi*, *Salvia sclarea L.*, *Valeriana officinalis*, *Rosmarinus officinalis*, *Coriandrum sativum* were assayed against *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *S. epidermidis* MRSA, *K. pneumoniae*, *Acinetobacter baumanii*, *Candida albicans* and other fungi. The results showed that all tested essential oils are active against all the microorganisms with differences between the strains. One strategy employed to overcome the resistance mechanisms is the use of combination of the essential oils of medicinal plants and conventional drugs. In addition, we investigated a possible synergistic effect of different essential oils in combination between them or with conventional drugs. The results show that some combinations are synergic. In conclusion, essential oils not only have antimicrobial activity but also can inhibit multidrug strains formation. Considering the huge increase in the number of multidrug resistant strains in health care facilities, essential oils may prove to be effective natural antimicrobial agents. Further studies will be necessary to assess the potential for therapeutic applications.

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Stampato da Tipografia Facciotti srl
Vicolo Pian Due Torri 74, 00146 Roma

Roma, ottobre-dicembre 2013 (n.4) 3° Suppl.