Chapter 25
Integrative Oncology: Scientific Research in Support of Patients: Useful, Possible, Valid

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Abstract The search for new anticancer drugs in the last years has shown its limits: no new molecule has been approved in recent years. Indeed, the last time we have seen the birth of only drugs "targeted therapy", which, as we know, are monoclonal antibodies. They are able to modify or block, starting from membrane receptors, intracellular signals, signal transduction pathways, without producing a persistent positive reaction towards neoplasia. In this situation came to rescue all natural medications with their active ingredients most suitable. Studies in Basic Searching the observations with traditional methods and the presentation of the first results of phase I and phase II are attracting a lot of attention. The discovery of the positive interaction use with chemotherapy and radiotherapy of substances such as polydatin, lactoferrin, boswellia serrata or curcumin and dozens of other natural substances has opened a new treatment scenario: the Integrative Oncology. The study of the possible synergistic interaction between chemotherapeutic drugs and natural substances has given rise to new researches. The Italian group of oncologists which belongs to the Association A.R.T.O.I. (Association of Integrative Oncology Therapies Research) had the strength and the courage to try these drugs integration. Observational studies have yielded first results of studies with Polydatin and AHCC. The benefit is visible through our treated cases.

The Integrative Oncology is the new reality for patients

Keywords Chemotherapy • Monoclonal antibodies • Natural substances • Integrative oncology

The incidence of neoplastic disease is increasing in all countries. So too are improved cancer therapies, but they carry an ever-increasing burden of suffering. Many patients are turning to their doctors to achieve better quality of life. Thus, a

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Table 25.1 The main clinical indications for which integrative oncology is used in European centers, in order of frequency

1	Reduction of adverse effects from chemotherapy and radiotherapy, with particular reference to nausea and vomiting
2	Management of pain
3	Reduction of adverse effects due to iatrogenic menopause
4	Improvement in quality of life
5	Resolution of anxiety, depression, fatigue; supportive treatment for chemotherapy and radiotherapy; perioperative noise reduction
6	Gastrointestinal disorders, sleep disorders
7	Prevention of relapse
8	Reduction of muscle disorders, palliative care, reduction of neuropathy

Table 25.2 Integrative oncology in Italy: ARTOI

Spreading of scientific knowledge
Scientific research
To integrate therapies and methodologies (hyperthermia)
To develop personalized therapy (pharmaco and nutrigenomic)
To improve results and quality of life
Prevention

new branch of cancer therapy has been created – integrated oncology – meaning a combined use of natural substances and methods that reduce side effects and improve survival. In Europe, the demand for integration is strong and reflects a whole series of requests for treatment that is not necessarily miraculous but at least able to reduce a whole series of problems as reported in Table 25.1. Among the methods found in Europe, acupuncture is the foremost, followed by traditional Chinese medicine (TCM), and herbal medicine. Integration is not the domain of simply a few oncologists. In America, Japan, China, and many parts of Europe, this method is so ingrained that it is taught in 52 universities. In Italy, no university teaches integrated medicine. Some public hospitals offer treatment with integrated therapies; however, these hospitals do not have dedicated integrated oncology units. However, some private hospitals do offer integrated oncology treatments, but this is affordable for only a few patients. To publicize this in Italy, a non-profit association (ARTOI; Association for Research on Integrated Oncology Therapies) has been created to disseminate knowledge, new methods, scientific research, guidelines on nutrition, and cancer prevention in the field of integrated oncology (Table 25.2).

Our perspective must change from one of ‘the tumor in the patient’ to one of ‘the patient with the disease’ being at the center of our work. In order to achieve this, we must select chemotherapy tailored more specifically to the patient, more targeted biological therapy, and natural substances for improved synergy, as well as involving psycho-oncology to improve patient compliance. Although we know that many anticancer drugs come from natural substances (Table 25.3) and that the next generation of monoclonal antibodies may provide benefit at affordable costs, with

Table 25.3 Orthodox chemotherapy: chemical substances synthesized in the laboratory

Extract of plants (taxanes)
Products of bacteria or fungi (antracyclins)
Alchilants substances (nitrosuree)
Composits of minerals (platinum)
Hormones

Table 25.4 Monoclonal antibodies

Substance	Name	Cancer	Price E	% result	
Erlotinib	**Tarceva**	Lung IV	4.600	2 month	ML20650, EURTAC
Gefitinib	**Iressa**	Lung IV	3.600	1.5 month	fase III ISEL
Cetuximab	**Erbitux**	Colon/head	600	15/70	CA225025-EMR 62 202-006
Trastuzumab	**Herceptin**	Breast-colon	1.000	35/10	MO16432-BO18225
Bevacizumab	**Avastin**	Breast-colon	2.000	10 month	*ECOG E2100-AVF2107g*
Rituximab	**Mabthera**	LNHodgkin	2.600	50/2 year	**M39021**
Pazopanib	**Votrient**	Kidney-sarcomas	1.800	3 month	VEG105192
Sunitinib	**Sutent**	Kidney IV	2.600	6–9 month	Fase III EORTC
Pertuzumab	**Perjeta**	Breast IV	4.500	6 month	CLEOPATRA
Lapatinib	**Tyverb**	Breast IV	1.800	2 month	EGF100151
Panitumumab	**Vectibix**	Colon IV	2.000	No results	Study of 1.189 pz
Ipilimumab	**Yervoy**	Melanoma IV	60.000	2 month	Fase 3 MDX010–20

Table 25.5 Plants with immunomodulatory activity

Tinospora cordifolia	Arabinogalactan, a. glucano
Whatania somnifora	Arabinogalactan
Astragalus membranaceus	Beta-glucans
Echinacea purpurea	Arabinogalactans, pectins
Glycyrrhiza glabra	Pectins
Panax ginseng	Arabinogalactans, pectins
Viscum album	Arabinogalactans, pectins
Aloe barbadensis	Acemannan
Panax quinquefolium	Arabinogalactan: alfa glucan
Lentinus edodes	

numerous side effects so serious as to stop treatment (Table 25.4); however, medium- and long-term results are not yet well known. We know the immunomodulatory action and antineoplastic activity (Table 25.5) of many natural substances (Table 25.6). The dilemma is to understand whether sufficient scientific evidence exists to combine them with an antineoplastic drug. One of the most important factors is to understand the pharmacokinetics of substances. We know that the main

Table 25.6 Natural Substances with anticancer activity

Apigenin	Licorice
N. acetil cisteine	Magnosalin
Curcumin (turmuric)	Omega-3 fatty acids
Epigallocatechin (green tea)	*Polypodium leucotomos*
Inosytol	Quercetin
Flavopiridol	**Resveratrol**
Ginkgo biloba	Red ginseng saponins (20(R)-and 20(S)-ginsenoside-Rg3)
Hydroxyflavones	Silymarin
Isoliquiritin	Torolin
Genistein (soy)	***Viscum album fermentatum***
Lactoferrin	*Selenium*
Beta-caroten	*Celecoxib*
Lycopens	***Sulforaphan***
Brassanine	*Indolo-3 carbinol*
Boswellia serrata	

pharmacokinetic mechanisms are related to absorption, distribution, metabolism, and excretion. Each of these mechanisms is important for optimum drug function: drugs must be ingested, inhaled, or infused into the body (absorption); they must be satisfactorily distributed to the various organs (distribution patterns); they must have a regular activation function (metabolism); and they must be regularly removed so as not to cause damage via accumulation (excretion). All these stages are important, but our main interest is in the metabolism of anticancer drugs and their interactions with natural substances that can affect induction and inhibition. An enzymatic induction action means that a substance may increase the metabolism of a drug, leading to reduced time in the bloodstream, and therefore a reduced pharmacological effect. Conversely, an enzyme inhibition action means that the drug will have reduced metabolism, much of it will remain in the bloodstream, with subsequent increased pharmacological effects, side effects and therefore toxicity. Whereas the enzymatic source of greatest interest is the cytochrome P450 (CYP) family and we know that 35 % of oxidation is carried out by CYP3A4, we also know that this enzyme metabolizes 70 % of anticancer drugs (Table 25.7). However, many natural substances have the same metabolic pathway as CYP, with inhibiting or inducing effects (Table 25.8). Therefore, we must be very careful when combining certain substances with chemotherapy (Table 25.9). We do know that many other substances interfere differently with anticancer drugs, increasing their action or reducing their side effects (Table 25.10).

Many scientific studies have investigated the use of herbal medicines and natural remedies (such as astragalus [McCulloch et al. 2006], honey [Abdulrhman et al. 2012], or American ginseng [Barton et al. 2010] as adjuvants to reduce side effects or improve response. We thoroughly understand the action of bovine lactoferrin – both its ability to inhibit angiogenesis and its ability to reduce the formation of intestinal polyps (Ligo et al. 2014) – and it is used as an antineoplastic

Table 25.7 Liver metabolism of anticancer drugs

Anastrozole	CYP2C9/CYP 3A4	Imatinib	CYP2C9/CYP 3A4
Bleomycin	N/A	Irinotecan	CYP 3A4/UGT1A1
Busulfan	CYP 3A4	Methotrexate	ABCC1/ABCG2
Capecitabine	Carbossilesterasi/Citidinesterasi	Mytomicine C	N/A
Cisplatin	OCT2/ABCC2	Oxaliplatin	OTC2
Cyclofosfamide	CYP2B6/CYP2C9/CYP3A4	Paclitaxel	CYP 3A4/CYP2C8
Docetaxel	CYP 3A4/5 – ABCB1	Tamoxifene	CYP2D6/CYP 3A4
Doxorubicine	CYP 3A4/CYP2D6-ABCB1	Teniposide	CYP 3A4 – ABCB1
Epirubicine	CYP 3A4	Topotecan	CYP 3A4 – ABCB2
Erlotinib	CYP3A4/CYP1A2	Vimblastine	CYP 3A4 – ABCB1
Etoposide	CYP3A4/ABCB1/ABCC1-2	Vincristine	CYP 3A4/5 – ABCB1
Fluorouracile	Diidropirimidin deidrogenasi	Vinorelbine	CYP 3A4
Gefitinib	CYP3A4/ABCG2		
Gemcitabine	Deamminasi		
Ifosfamide	CYP2B6/CYP3A4		

Table 25.8 Liver metabolism (inducer or inhibitor) of natural substances

Panax ginseng	**Inhib**.CYP2D6/ CYP3A4	Vitis vinifera	**induct.** CYP3A4
Citrus aurantium	**no az.CYP2D6/ CYP3A4**	Tea green	**no act CYP2D6/CYP3A4 Induct.** CYP1A2
Black pepper	**Inhib.**CYP3A4/ ABCB1	Kava kava	**strong inhib.** CYP2E1
Scutellaria	Inib. CYP3A4/ ABCB1	Licorice	**inhib**. CYP3A4
Echinacea	**Induct**. CYP3A4	**Silibum mariano**	**no act CYP1A2 CYP2D6/CYP3A4**
Garlic	**Inhib** CYP3A4/ CYP2E1		
Ginger	**no act CYP2C9**	Peppermit	**Inhib.** CYP3A4
Grapefruit	**strong inhib.** CYP3A4	**Panax quinq**	**no az CYP2D6/CYP3A4**
Ginkgo	**strong induct**. CYP2C19	S. Jont W	**strong induct.** CYP1A2/CYP2C8/ CYP2C9/CYP2E1/CYP3A4
	Inhib CYP3A4	**Turmeric**	**no act CYP3A4**
		Valerian	**no act CYP1A2/CYP2D6/CYP3A4**
		Alfa glucan	**no act CYP1A2/CYP2D6/CYP3A4**

agent in lung cancer that has progressed after chemotherapy. We know a lot about the action of epigallocatechin gallate on cell cycles, its association with induction of apoptosis, reduction of angiogenesis, and blockage of platelet-derived growth factor (PDGF), and that it can be used with a monoclonal antibody such as erlotinib on tumors of the head and neck, or in mammary tumors as a new antineoplastic

Table 25.9 Attention, discourage or avoid use of natural substances during chemotherapy

ECHINACEA	**Attention** with camptothecins, cyclophosphamide TK inhibitors, epipodophyllotoxin, taxans, vinca (inductor CYP3A4)
GINKGO	**Attention with** camptothecins, cyclophosphamide taxans, vinca (inhibitor CYP3A4/CYP2C19)
	Discourage alkylanting agents, cancer antibiotics, platinum derivates (scavenger with free radicals)
GINSENG	**Discourage** estrogen receptor-positive breast and endometrial (stimulus to growth)
GREEN TEA	**Discourage** with erlotinib (CYP1A2 inductor)
SOY	**Avoid** with tamoxifen (antagonist in inhibiting growth), estrogen receptor positive, breast- endometrium (stimulus to growth)
St. JOHN W	**Avoid with all drugs** (inductor of all CYP)
VALERIAN	**Attention** with tamoxifen, cyclophosphamide, teniposide (CYP2C19 inhibitor)
VITIS VINIFERA	**Attention** with camptothecins, cyclophosphamide TK inhibitors, epipodophyllotoxins, taxans, vinca, platinum (inductor CYP3A4 e scavenger with free radicals)

Table 25.10 Natural substances with positive co-treatment with chemotherapy

Drugs	Increased antineoplastic action	Reduction toxicity
Cisplatin	Quercitin	Coriolus versicolor
	Astragalo membranaceus	Silibum mariano
	AHCC	AHCC
	Aloe vera	Ginkgo biloba
Cyclophosphamide		Astragalo membranaceus
Gemcytabine	Curcumin/viscum album	AHCC
		Withania somnif.
		Coriolous versic.
Adriamycin/Idarab	Green tea	Green tea
		AHCC
Fluorouracil/Il-2	Turmenic	AHCC
	Green tea/astragalo	
	Panax ginseng	
Tamoxifen	GreeTea/panax quinqu.	
Mitomycin C	Panax ginseng	
Taxol	Curcumin	AHCC

strategy in combination with anticancer drugs (Sugamuna et al. 2011). The primary actions of sulforaphane, extracted from Brassicaceae, are to block histone deacetylase and angiogenesis and to stimulate the immune system (T cells, natural killer [NK] cells, and dendritic cells). Curcumin has multiple actions: modulation of

cyclin D1 and C-Myc, increase cell survival, and Bcl-2, caspase activation 3-8-9-, signal transduction by c-June N-terminal kinases (JNKs), protein kinase B (AKT), AMP-activated protein kinase (AMPK), stimulation of apoptosis by p53 and p21; however, its primary action is in the blocking of nuclear factor (NF)-κB.

Phase I and II studies have also investigated the combined use of curcumin and gemcitabine in patients with pancreatic cancer; the results are very encouraging (Epelbaum et al. 2010). Boswellia serrata is a natural substance with the ability to pass the blood brain barrier and block two genes of neoplastic proliferation cerebral (COX-2 and 5-LOX). Very important results have been seen in the reduction of cerebral edema (Kirste et al. 2011). Resveratrol and polydatin come from the same plant family but have different absorptions: polydatin shows a capacity that is ten times higher than that of resveratrol, even when a much lower dosage is used. It is an anti-inflammatory pro-apoptotic and regulates the immune system. It also exceeds the BEE, contributing at an interstitial level (De Maria 2013). Not all countries can afford large expenditure on anticancer drugs; therefore, many nations have developed scientific studies using low doses both of chemotherapeutic drugs and of natural substances (so-called low-dose therapy). Low doses of Ruta graveolens and Calcarea phosphorica have been used in a study of high-grade brain lesions (glioblastomas). Study data on the use of these substances in glioblastoma report survival to be higher than that in the literature. Based on these studies and knowledge of natural substances, an observational study investigated some cases of primary high-grade brain lesions, and brain metastases from primary breast cancer. Integrated treatments have seen the use of Boswellia serrata, polydatin, curcumin, Ruta graveolens, and Calcarea phosphorica in association with radiotherapy and/or chemotherapy whenever possible. The results have been very encouraging (secondary brain injury from primary breast cancer disappeared in two cases, recurrent glioblastoma was absent in three cases for more than 30 months, the clinical picture stabilized over 24 months in two cases of glioblastoma, a patient with malignant oligodendroglioma was disease free for over 6 years).

Clinical data are interesting, but further study is certainly required before considering this type of treatment as a standard for the disease. Very interesting data have arisen in two other observational studies that used two new molecules: polydatin and an alpha-beta glucan (active hexose correlated compound [AHCC]). AHCC, a natural substance extracted from the mycelium of shitake grown on a base of fermented rice, is much used and appreciated pharmacologically in Japan (Ishiguro et al. 1999). It affects the control of neoplastic cell growth and the immune system. A group of 43 patients was split in two: one group received a daily dose of 3 g and the other group received a daily dose of 6 g. In the first group, no relapses were observed at 1-year follow-up. In the second group (in which

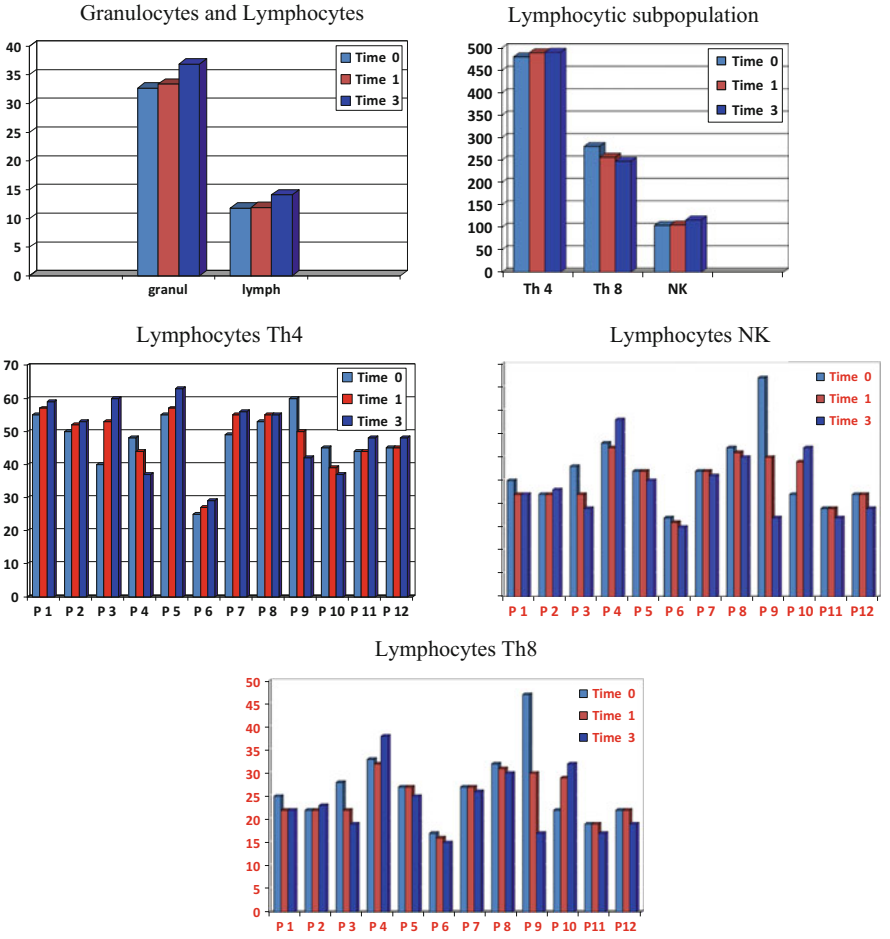

Fig. 25.1 Change in blood levels of the immune system with administration of AHCC

neoplastic lesions were present at the beginning of the study), three patients experienced a reduction in metastases, and hepatic lesions disappeared in one of these. In terms of laboratory tests, we observed a direct correlation between improvement in quality of life and increases in Th4 lymphocytes (helper), reduction in Th8 (suppressor), and normalization of NK cells (Fig. 25.1). The second observational study used polydatin. This natural substance is a piceid; it has a glycosidic part that allows for better transmembrane transport than resveratrol. Inside the cell, it then behaves like a stilben-resveratrol, albeit using different transduction pathways (Ravagnan et al. 2013). In this study, 49 patients were observed: 24 were treated with chemotherapy/radiotherapy and were free from neoplastic disease; the other 25 patients instead showed ongoing pathology. We administered polydatin 160 mg in the first group and 240 mg in the second group. Again, at 3-month and

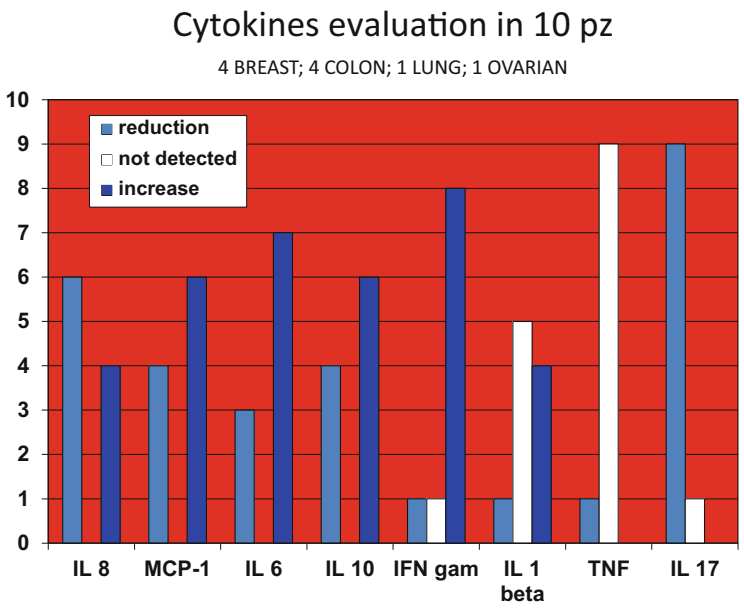

Fig. 25.2 Types of Cytokines involved with administration of Polydatin

1-year follow-up, we noted improvements in immune system activity (Th4 increased, TH8 decreased, and NK increased) in both groups, with a reduction of neoplastic lesions in 11 patients, with liver lesions disappearing in three patients. We went to see which types of cytokines were also involved. Results indicated that interferon gamma and interleukin (IL)-6 had increased, and IL-8 and IL-17 had decreased (Fig. 25.2).

We also wondered if there could be some economic advantage in the use of natural substances. In the 14 patients in whom neoplastic lesions reduced or disappeared, the use of hematopoietic growth factors was markedly reduced, with a net saving of €30,000 in 3 months. As we can see in the final analysis, the use of natural substances in cancer can not only reduce the side effects of chemotherapy or radiotherapy (made possible by the lack of interference with anticancer drugs), but it is also possible to reduce healthcare spending. Often there is also a clinical benefit in improving patient response against neoplastic disease. Natural substances can reduce neoplastic disease such that prognosis may become more manageable – and thus can be most rightly named 'integrated oncology'. As we say in ARTOI: learn to care for the better . . . and to keep dreaming.

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