The Di Bella Method (DBM)

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Submitted: 2010-03-18 Accepted: 2010-05-18 Published online: 2010-09-29

Key words: **Di Bella Method; somatostatin; octreotide; melatonin; retinoids; vitamins E, C, D3; chondroitin sulfate; calcium; Bromocriptin; Cabergoline**

Neuroendocrinol Lett 2010; **31**(Suppl.1):7–42 **PMID:** 20881933 NEL310710A01

Abstract

AIMS: the aim of the Di Bella Method (DBM) is to try to overcome the high toxicity level and the limited efficacy of the current medical treatments for cancer.
METHOD: using Melatonin, Retinoids, and vitamins E, D3, and C, components of the extracellular matrix, the DBM reinforces those means that Physiology considers essential for life. Acting together, these differentiating molecules also have an antiangiogenic and antiproliferative effect. Cabergoline and/or Bromocriptin negatively regulate Prolactin, the ubiquitary mitogenic hormone. This effect is reinforced by Somatostatin and/or its analogues by negatively regulating highly mitogenic molecules such as GH and GH-dependent growth factors.
RESULTS: the preliminary results are reported of a retrospective observational study on 553 patients treated with the DBM. These data show that the DBM achieved an evident improvement in the quality of life and a considerable increase in the mean survival rates for every disease and stage with respect to the data available in the literature relative to chemotherapy and/or monoclonal antibodies. The result was achieved without any of the known significant toxic effects of chemotherapy and (albeit to a lesser extent with respect to chemotherapy) of monoclonal antibodies. The invalidating causes which removed all scientific credibility from the DBM experiments carried out in Italy in 1998 are also reported.
CONCLUSIONS: I considered it of use to inform the scientific community of the rationale, the mechanism of action, the scientific basis and clinical findings of the DBM in order to encourage interest in the prospects opened up by the DBM through innovative formulations of the vitamins and Melatonin and the use of biological molecules with a high degree of antitumoural efficacy and low toxicity such as Somatostatin and its analogues.

Conflict of Interests Statement: Dr. Giuseppe Di Bella is the President of the Di Bella Foundation – a non-profit organization. The author declares no conflict of interest.

Abbreviations:

ATRA	- All Trans Retinoic Acid
CCK	- Cholecystokinin
C.M.	- GH-induced monocyte chemotaxis
CTU	- Technical expert
MDB	- Di Bella's Method
EGF	- Epidermal Growth Factor
EGFR	- Epidermal Growth Factor Receptor
FGF	- Fibroblastic Growth Factor
G	- Gastrin
GF	- Growth Factor
GH	- Growth Hormone
GHR	- Growth Hormone Receptor
HGF	- Hepatocyte Growth Factor,
IGF1-2	- Insulin-like Growth Factor 1-2
IGFR	- Insulin-like Growth Factor Receptor
IL8	- Interleukin 8
MRI	- Magnetic Resonance Imaging
MLT	- Melatonin
NGF	- Nerve Growth Factor
NHL	- Non-Hodgkin's Lymphoma
NOSe	- endothelial Nitric Oxide Synthase
PDGF	- Platelet-Derived Growth Factor
PET	- Positron Emission Tomography
PG2	- Prostaglandin 2
SSN	- National Health Service
SST	- Somatostatin
SSTR	- Somatostatin Receptor
TGF	- Transforming Growth Factor
TRK	- Tyrosine-kinase
VEGF	- Vascular Endothelial Growth Factor
VIP	- Vasoactive Intestinal Peptide

INTRODUCTION

The rationale, the aims, the components, the biochemical and physiological bases and the molecular biology mechanisms of action of the DBM are described. The tolerability, the clinical findings and the confirmation in the literature of the antitumoural efficacy of each individual component of the DBM, enhanced by the synergic factorial effect, are reported. The serious numerous irregularities that totally delegitimised the DBM experiments in 1998 are also pointed out. The positive results achieved with the retrospective observational study on patients treated with the DBM are reported.

The current data in the literature on chemotherapy document a high degree of toxicity and a mortality percentage also reported by the Reuters Health Agency (Wesport, CT 2001-05-17): "Unexpected high mortality rates associated with chemotherapy regimen..". This is confirmed by a study of the chemotherapy protocols for lymphoproliferative diseases (Atra et al. 1998) which reports a mortality rate of 11%, not caused by the tumour but solely by the chemotherapy.

The current survival of patients with tumours is mainly due to surgery, much less to radiotherapy, reaching 29% at 5 years (Richards et al. 2000). Of this 29%, only 2.1–2.5% is due to chemotherapy (Morgan et al. 2005). This fundamental publication is based on 14 years of observation, 225,000 patients and 22 types of tumour, aimed at ascertaining the true contribution of chemotherapy in achieving 5 years of survival.

Chemotherapy alone, without surgery, thus allows only 2.1–2.5% of patients to survive for 5 years, after which it has been ascertained that half of these patients who have survived for five years will die in the long-term as a result of their tumour (Lopez et al. 1998). Data from the recent conferences of the American Society of Clinical Oncology clearly show that in solid tumours monoclonal antibodies allow an average increase in survival of around two months, and only in rare cases, with or without associated chemotherapy, does this figure rise to or exceed four months

Based on these data reported in the literature, we decided that it was appropriate to propose the new biological, physiological and rational therapy protocols of the DBM with greater efficacy and lower toxicity.

METHOD

Treatment (components of the DBM)

The DBM consists of:

A) a fixed part, acting on the common denominators of all tumours.
B) a variable part, according to the specific tumour characteristics.

A) FIXED PART

Consisting of the following components

1) **All-Trans Retinoic Acid**
   Axerophthol palmitate
   Betacarotene
   Alpha tocopheryl acetate

These molecules are mixed in solution form, a formulation that allows maximum bioavailability, in these ratios:

All-Trans Retinoic Acid	0.5 gr
Axerophthol palmitate	0.5 gr
Betacarotene	1 gr
Alpha tocopheryl acetate	1,000 gr

The daily dose is based on body weight decimals: an adult weighing 70 kg can take 7 grams of solution 3 times a day.

2) Melatonin tablets, Prof. Di Bella's formulation, chemically complexed as follows: Melatonin 12% Adenosine 51%, Glycin 37%, administered in doses of from 20 to 60 mg per day.

Bromocriptin 2.5 mg tablets, one tablet per day divided into ½ in the morning and ½ in the evening.

Cabergoline 0.5 mg tablets. This can be used with or instead of Bromocriptin, taking ½ a tablet twice a week.

Dihydrotachysterol, synthetic Vit D_3, 10 drops before meals together with the retinoid solution 3 times a day.

Chondroitin sulfate, one 800 mg sachet morning and evening dissolved in water.

Cyclophosphamide 50 mg tablets, one or two per day.

Hydroxyurea 500 mg tablets, one or two per day as an alternative to cyclophosphamide.

Somatostatin, peptide with 14 amino acids, 3 mg per day, injected slowly in the evening after supper, subcutaneously or intravenously with a 12-hour timed syringe (evening administration is indispensable since this coincides with the nocturnal peak in GH and GH-dependent growth factors).

Octreotide, peptide with 8 amino acids, in ***a*** 1 mg ampoule/day administered as above (alternatively, the delayed formulation of Octreotide can be administered intramuscularly at the same doses).

Vit. C, 2–4 grams per day, orally.

Calcium, 2 grams per day, orally.

B) VARIABILE PART

This includes the following components:

- **Androgen inhibitors** in hormone-dependent tumours in males.
- **Estrogen inhibitors** in hormone-dependent tumours in females (excluding Tamoxifen due to the possible thromboembolic and neoplastic induction complications).
- **Synthetic ACTH**, tetracosactide hexa-acetate, polypeptide with 24 amino acids, with the same indications as cortisone, used as a replacement of cortisone due to its better ratio between tolerability and efficacy. Dosage of 1 mg per week intramuscularly, depending on pressure, blood sugar and electrolytic homeostasis.
- **Glyphosine** (N,N-Bis(phosphonomethyl)glycine) 200 mg capsules, twice a day, orally, in primary or secondary tumours of the osteocartilaginous tissue.
- **Isoniazid**, one 200 mg capsule a day, in lung tumours or cancer of the bladder.
- **Anhydromethylencitrate of hexamethylentetramine,** 10% watery solution, one dessertspoon 3 times a day (at meals) in HCV-correlated hepatocarcinoma.
- **Dibromomannitol** in thrombocythemia. Used in microdoses of about 30–40 mg, on alternate days.
- **Human albumin** at 20–25% in 50 ml intravenously in disproteinemia and in pleural and ascitic effusion
- **Lenograstim,** or **Filgrastim**, white cell growth factors, in leucopenia, administered subcutaneously or intravenously until physiological values are restored.
- **Erythropoietin** in anemic conditions, associated in iron-deficiency anemia with iron orally or intravenously and folates.
- **Lysozyme** 500 mg tablets, 5–6 gram per day, in concomitant infectious diseases, for its antiviral, antibacterial and atoxic antiprotozoic effect and immunitary reinforcement.
- **Immunoglobulin**, 5 ml intramuscularly per day (in concomitant infectious diseases) for immunitary reinforcement,
- **Phenyl-quinoline-carbonic acid** 1,000 mg orally, morning and evening on the 1st day, one gram once a day on the 2nd and 3rd day, together with 2 litres per day of mineral water. At these doses, phenyl-quinoline-carbonic acid rapidly normalises uricemia with a decidedly more favourable toxicity/benefit ratio compared to the monoamine oxidase inhibitors commonly used in these situations. Chronic administration of these inhibitors blocks enzymatic chains with a high functional level and can cause other serious diseases.
- **Taurine,** 200 mg capsules, twice a day to activate the choleretic and cholagogue effect and blood-tissue exchanges.
- **Selenium methonine,** 40 μg capsules, twice a day, with antioxidant free antiradical action.
- **Calcium levofolinate,** 22 mg capsules, one a day, for its differentiating and myeloprotective action.

ANTITUMOURAL MECHANISMS OF ACTION OF THE COMPONENTS OF THE DBM

Retinoids

Betacarotene

- Has a protective effect on the cellular membranes (Di Bella, 1998)
- Reduces lipid peroxidation and increases Glutathione (Basu et al. 2000)
- Has a direct antiproliferative effect (regardless of its conversion to ATRA) on the tumour cells, significantly suppresses both the mobility (measured by MTT tetrazolium) and synthesis of DNA (controlled by incorporation of 3H-thymidine) and cell proliferation (measured by cell count) (Onogi et al. 1998).

Vit. A (Axerophthol or retinol)

- Causes tumour cell death by apoptosis, through activation of proteolytic cellular enzymes, the caspases, and degradation of the general transcription factor Sp-1 (Piedrafita et al. 1997).

Retinoic acid (All Trans Retinoic Acid –A.T.R.A.)

- Acts by redifferentiating blasts and tumour cells (Hassan et al. 1990)
- Induces the synthesis of leukotriene C4 (Abe et al. 2003)

- Suppresses the genetic transcription of oncogenic factors and promotes the antiproliferative effect (Arnold et al. 1994)
- Has an anti-angiogenetic action (Majewski et al. 1994)
- Decreases the microvascular density of the bone marrow, in leukemia, and the hot-spot density. Interrupts the production of VEGF by the **NB4 cells**, by suppressing angiogenesis (Kini et al. 2001)
- Stops the cellular development associated with the increase in levels of interferon 1 (IRF-1) with activation of p21WAF1 (Arany et al. 2003).
- Activates apoptosis, with the contribution of IRF-1 and STAT1, by means of caspase 1 (Arany et al. 2003).
- Stops the progression of the cellular cycle (Wu et al. 2009).
- Induces a halt of the cellular cycle in G0/G1 (Wu et al. 2009).
- Induces the expression of p21 WAF1/CIP 1, through p 53 dependent and independent pathways (Wu et al. 2009).
- Inhibits activation of the activator protein-1 (AP-1) in the tumour cells, by means of its receptor RAR-alpha and activates the expression of cJun and cFos (Wu et al. 2009).
- Synergizes the effect of Bcl-2, on stopping growth and on expression of the gene p21 (Chou et al. 2000).
- Prevents invasion of colon cancer cells and decreases the expression of matrilysin (Adachi et al. 2001).
- Causes morphological and biochemical changes in the tumour cells, such as shrinkage of the membrane, condensation of chromatin and breakage of DNA, typical characteristics of cells during apoptosis (Lee et al. 2008).
- Activates a net increase of c-myc and Bax proteins by means of RAR-beta, increasing susceptibility to apoptosis (Lee et al. 2008).
- Decreases the potential of neoplastic proliferation and has an important role in differentiation, apoptosis and cellular adhesion (Voigt et al. 2000).
- Makes the tumour cells particularly sensitive to chemotherapy agents, also inducing an increase in intercellular communication in the junction spaces (Carystinos et al. 2001).
- Reduces the level of glial fibrillary protein with silicon and the synthesis of DNA, and induces apoptotic processes, demonstrating notable synergism and reinforcement of the efficacy with TNF-alpha by an increase of the p55 TNF receptors (Chambaut-Guerin et al. 2000).
- Induces a gene, autotaxin (ATX), which decodes a stimulation factor of the tumour motility (Duffner Beattie et al. 2001).
- Induces neurotic differentiation with extensive growth of the neurites, reduction of the oncoprotein n-Myc and of the mRNA of Gap-43. Exerts its antiproliferative effect through the increase of kinase A of the type II/RII beta protein and kinase A of the W protein (Kim et al. 2009).
- Differentiates the tumour cells through its effect on the Ca2+-dependent A2 phospholipases (Antony et al. 2009).
- Reduces the expression of VnR, correlated with the organisation of fibronectin and with cellular adhesion and expansion (Baroni et al. 2003).
- Reduces the chemically induced inhibition of RAR Beta by blocking the cellular cycle in the G1 phase (Song et al. 2001).

Vitamin E

Inhibits the growth of various tumour cell lines, such as:

- Prostate cancer cells (Israel et al.2000; Yu et al..2002; Zhang et al. 2002)
- Breast cancer cells (Yu et al. 1999; Pussinen et al. 2000; Yu et al. 1999)
- Lung cancer cells (Neuzil et al. 2001)
- Parotid cancer cells (Prasad et al. 1996)
- **Stomach cancer cells** (Rose et al. 2001; Wu et al. 2002)
- Colon cancer cells (Neuzil et al. 2001)
- Pancreas cancer cells (Heisler et al. 2000)
- Oral squamous cancer cells (Elattar et al.1999)
- Melanoma cells (Prasad et al. 1990)
- Neuroblastoma cells (Prasad et al. 2003)
- Glioma cells (Prasad et al. 2003)
- Leukemia cells (Yamamoto et al. 2000)
- Lymphoma cells (Turley et al. 1995; Yu et al. 1997; Dalen et al. 2003)
- At low doses, induces differentiation and inhibition of tumour proliferation; at higher concentrations, induces apoptosis (Prasad et al. 2003)
- Suppresses tumour growth (Prasad 2003)
- Apoptotic and/or cytostatic action on breast cancer cells (Malafa et al. 2000)
- Colon cancer cells (Prasad et al. 2003)
- Melanoma cells (Malafa et al. 2002)
- Neuroblastoma cells (Prasad et al. 2003)
- Lymphoma cells (Sarna et al. 2000)
- Reinforces the antitumoural action of various chemotherapy agents such as adriamycin, cisplatin and tamoxifen (Ripoll et al. 1986; Prasad et al. 1994)
- Protects bone marrow cells from the lethal effects of doxorubicin (Fariss et al. 1994).
- Reinforces the antitumoural effect of chemotherapy agents, protecting the healthy cells from the toxic effects (Prasad et al. 2003)
- Antiangiogenetic activity (Shklar et al. 1996; Tang et al. 2001; Neuzil et al. 2002; Inokuchi et al. 2003; Miyazawa et al. 2004).

Melatonin (MLT)

- Anti-platelet aggregation action (Di Bella et al. 1969; Di Bella et al. 1979; Di Bella et al. 1980)
- **Reduces the transcription of the estrogen receptor, blocks the mitogenic action of prolaction and the blastic effect induced by the epidermal growth factor (EGF)** (Bartsch et al. 2001).

- Contributes to the synthesis of NO-synthase, reinforcing its complex activity, including the antitumoural effect, probably in synergy with Ca-modulin, tyrosine kinase and tumour necrosing factor (TNF). In this series of reactions which lead to the production of NO and polyamines, MLT can play a fundamental role (Di Bella 1998).
- Modulates the hypophysis-gonadic, and immunitary activity, and the antitumoural "scavenger" action (Di Bella 1998).
- Interacts with the tumour biology in many different ways and mechanisms (Di Bella 1997).
- Ubiquitous availability of the phosphoric esters of AMP, ADP and ATP (Di Bella 1998).
- Within the framework of the DNES (Diffuse Neuroendocrine System) it has an irreplaceable role in stimulating the systemic response and control for protection of the body, acting in all organ systems (Kvetnoi et al. 2002)
- Represents the key molecule of the paracrine system for local coordination of intercellular reactions (Kvetnoi et al. 1994).
- In a physiological, homeostatic form, the body tends to normalise or limit the pathological proliferative processes through MLT (Bartsch et al. 1997).
- The production of MLT and the relative APUD peptides, in situ, in non endocrine cancers, plays a determining role in the autocrine mechanisms of antitumoural homeostasis (Kvetnoi et al. 1986)
- Reduces the incidence of hyperplastic alveolar nodules and the presence of the N-ras protein in focal hyperplastic lesions; also effectively prevents the atypia of the epithelial cells and adenocarcinoma of the breast, in which it also reduces the hyperplasia of the lymphoid tissue (Mediavilla et al. 1999).
- Represents the key molecule of the paracrine system for local coordination of intercellular reactions (Maestroni et al. 1988).
- The plasma level of MLT is inversely proportional to the proliferative index of the tumours, immunohistochemically determined by the presence of the nuclear antigen of the proliferating cells (Bartsc et al. 2001).
- Antagonizing effect on the prolactin-dependent growth of human breast cancer (Lemus-Wilson et al. 1995).
- Inhibiting effect at physiological doses on DNA synthesis in tumour cells (Cos et al. 1996).
- Exerts its antitumoural function also on the intercellular junction spaces, inducing the protein of the CX32 junction space (Kojma et al. 1997)
- Activates the polymerization process of tubulin at intercellular level. At physiological concentrations, induces an increase of microtubules in the tumour cells (Melendez et al. 1996).
- Increases radiosensitivity and has stabilizing effects on the metabolic disorders that develop during the oncological process, has immunomodulating action, activates the cytotoxic function of natural-killer lymphocytes and the production of interferon (Kvetnoi et al. 1986)
- Has a radioprotective action and has been shown to have radiomodifying and radiosensitizing properties (Lissoni et al. 1996).
- If administered before radiotherapy, reduces the hepatic damage caused by ionizing radiation. Its radioprotective action takes place through inactivation of the free radicals produced by ionizing radiation (Taysi et al. 2003).
- It protects the nerve cells from the oxidative stress caused by cobalt and neurotoxicity and increases the secretion of beta amyloid (Olivieri et al. 2003).
- Prevents and delays chemical carcinogenesis (Hrushesky et al. 2009).
- In tumour patients, simultaneously and rapidly inhibits both the release of fatty acid from the adipose bodies and the absorption of fatty acid by the tumours (Sauer et al. 2001).
- Has an antiradical effect synergic with that of Vit. E, and protects the entire cell from oxidative stress by various means, including the reinforcement of enzymatic systems such as glutathion-peroxidase, the increase in mRNA synthesis and consequently superoxide dismutase. Inhibits lipid peroxidation, with an effect synergic with the retinoids. Reduces the incidence of mutations and thus the probability of cancer (Reiter et al.2000).
- Inhibits the secretion of mitogen factors such as prolactin (Lemus-Wilson et al. 1995).
- Through the **mel1** receptors has a direct antiproliferative effect on the androgen-sensitive LNCaP cells of human prostate cancer (Xi et al. 2000).
- Regulates various secondary messengers: cAMP, cGMP, diacylglycerol, inositol, and Arachidonic acid and the intracellular concentration of Ca2+. Also regulates the transcription factors, i.e. phosphorylation of the binding protein, an element which responds to cAMP and the expression of c-Fos. Activates mechanisms which inhibit adenyl cyclase and modulate the metabolism of phospholipids and (Ca2+O) (Vanecek 1998).
- In thalassemia patients it improves the synthesis of Hb and slows down its degradation, also increasing globular resistance(Di Bella 1998, Di Bella, 1980).
- Synergic antiproliferative effect of MLT and Vit. D_3 with ability of the two molecules to inhibit cellular proliferation in a dose-dependent way, expressing a reciprocal and highly significant reinforcement also in the increase of the expression of TGF-beta which contributes to blocking proliferation (Bizzarri et al. 2003).
- Mobilizes the AR (androgen receptor) from karyosol to cytosol and limits its expression, thus limiting the epithelial responses to the androgen (Rimler et al. 2002).
- Acts as a chronobiological oncostatic able to control cell proliferation and activate apoptosis (Blask et al. 2002).
- Inhibits estrogen-dependent tumours, reducing the expression and transcription of the estrogen

receptor, the patency of the ionic channels of the cell membranes to calcium, the activity of protein kinases, the cytoskeletal architecture and functionality, the transport, metabolization and use of linoleic acid and other fatty acids by the tumour cells. Suppresses EGFR (epidermal growth factor receptor) (Blask et al. 2002).

- Reversibly inhibits neoplastic proliferation while increasing the expression of the proteins P53 and P21 WAF 1, regulates the cell cycle and incidence of metastases through expression of the E-cadherin and beta-1 integrin proteins; also reduces the expression of ER and the DNA response to the ER complex (Pawlikowski et al. 1999–2002).
- Inhibits the metastatic spread of the tumour cells. This is achieved by a reduced attraction for fibronectin (Mediavilla et al.1999).
- Increases the life expectancy of tumour patients to a considerable degree, improving their quality of life (Lissoni et al. 1999)
- Contains the processes which lead to neoplastic cachexia (Lissoni et al. 1999)
- Reduces the toxicity of chemotherapy (Lissoni et al. 1999)
- The quantity of tumour cells that the tissues can process and release is conditioned by the inhibiting antitumoural function of MLT and by its concentration in the blood and in the tissues (Di Bella 1997).

Somatostatin and analogues

- Increases the expression of mouse isomerase, inhibiting the proliferative tumour cell cycle (Brevini et al. 2001).
- Inhibition of the non-oxidative pathways of pentose phosphate (Boros et al. 1998).
- Inhibition of the carbon cycle recycling through PC of 5.7%, with a 19.8% increase in combination with oxythiamine (Boros et al.1998).
- Regulation of the ionic channels, inhibition of adenylcyclase, kinase, serine/threonine phosphatase and thyroxine phosphatase (Bousquet et al. 2001).
- Marked increase of the activity of adenylate cyclase (Giannetti et al. 2000).
- Inhibition of DNA synthesis (Charland et al. 2001).
- Antiproliferative effect by suppressing the reduction of p27 (Baradari et al. 2006)
- Induction of the expression of $p21^{Cip}$, inhibition of the phosphatidylinositol 3-kinase, and a greater expression of $p21^{Cip}$ and $p27^{Kip1}$, which leads to repression of the phosphorylation of pRb and of the complex activity of cyclin E-cdk2 (Charland et al. 2001).
- Inhibition of the incorporation of 3H-thymidine in the DNA of the tumour cells (Yano et al. 2000; Feind et al. Damge et al. 1998).
- Significant reduction of IGF-1 (Ingle et al. 1999).
- Dose-dependent inhibition of tyrosine phosphorylation, by EGFR (activated by EGF) (Mischima et al. 1999).
- Induction of intracellular PTP1C translocation to the tumour cell membranes (Srikant et al. 1996).
- SSTR-mediated induction of the protein-tyrosine phosphatase (PTP) activity, implicated in antiproliferative signalling for its dephosphorylating activity and for inactivating the kinases of the growth factor receptor (Srikant et al. 1996).
- Inhibition of PTPase and PTP1C, and of the tyrosine kinase activity of the membrane and of p 42MAP kinase (Douziech et al. 1999).
- Reduction in the tumour cells of epidermal growth factor receptors (EGFR) (Szepeshazi et al. 1999).
- Positive and stimulating effect on Kupffer cells, with antitumoural mechanism, reinforced by a marked inhibition of hepatic lipid peroxidation (Kouroumanlis et al. 2001).
- Apoptotic effect with nuclear condensation of chromatin and cell fragmentation and shrinking, and formation of apoptotic bodies, with a directly proportional, dose-dependent correlation between somatostation concentration and apoptotic rate (Che et al. 2009).
- Inhibition of the S phase of the cell cycle with dose-dependent apoptosis induction, increase in intrametastatic lipic peroxidation, with loss of tumour cell integrity (Raderer et al.2000).
- Destruction of the plasma concentrations of tumour growth factors such as IGF-1 and EGF with statistically significant decrease of the S phase percentage (Cascinu et al. 1997).
- Increase in the activity of the suppressor gene p53, with inhibiting ability on the tumour lines, totally independent of the status of their p53 (Szepeshasi et al. 2002).
- Reinforcement of the chemotherapy agent effects on tumours (Tesei et al. 2000).
- Inhibition of the kinase activity of the mitogen-activated protein (MAP) (Cattaneo et al. 2000).
- Intense phosphatase activity (Cattaneo et al. 1996).
- Suppression of Ras activation induced by PDGF (Cattaneo et al. 1999).
- Induction not only of apoptosis but also of CA (chromosomal aberration), i.e. chromosomal breakage with decided antiblastic effect (Tompa et al. 2000).
- Induction of the migration of AML cells by activation of SSTR-2 and attraction to the normal hematopoietic progenitor cells of chemotactic factors, with implications in the distribution of AML cells in the body, with clinical applications in acute myeloid leukemia (Oomen et al. 2001).
- Activation of tyrosine phosphatases, of SHP2 protein and inhibition of the kinases of the mitogen-activated protein (Held Feind et al. 2000).
- Significant dose-dependent inhibition of the proliferation of leukemia cells with reduction of the expression of the c-fos gene(Ishihara et al. 1999).
- Induction of a strong expression of the bcl-2 protein with relative apoptotic effect (Zalatnai et al. 1999).

- Decrease of the cells in S phase and of the dose-dependent proliferative index (Raderer et al. 2000).
- Decrease of the serum levels of in hepatocarcinoma (Raderer et al. 2000).
- Dephosphorylation of the kinases of the mitogen-activated protein ERK 1-2 (Held Field et al. 2001).
- Reduction of the expression of EGF stimulated by the AP1 complex at transcriptional and translational level (Held Field et al. 2001).
- Proapoptotic and antiproliferativ effect in synergy with MLT (Melen-Mucha et al. 1998).

Vit. D_3 and analogues

- Induction of differentiation and apoptosis, and proliferative block of progression to the S phasee due to appearance of the hypophosphorylated form of the retinoblastoma protein (pRb), inhibiting growth and modulation activity of the cyclin-dependent kinases (cdk) 2-4-6 (Jensen et al. 2001).
- D_3 prevents activation of the D1cdk-4 cyclin, and the loss of cyclin D3, which together lead to the loss of transcription factors of E2F, inhibiting the expression of the A protein of cyclin. Together with a rapid decrease of the oncoprotein c-Myc in response to D_3, these results demonstrate that D_3 blocks proliferation by intervening on the key regulators of G1-S transition (Jensen et al. 2001).
- Pro-differentiating activity of D_3, which takes place not only by interacting with the receptor but also by extra-receptorial mechanisms mediated by the membrane (Marcinkowska 2001).
- Inhibition both of the expression of PTHR in bone by decreasing its transcription by means of P2, and of the transcription of the PTHrP gene. This is clinically significant in preventing the serious damage produced by the hypercalcemia induced by the excess production of PTHrP in the tumour cells (Goltzman 2001).
- Dose-dependent inhibition of angiogenesis, of the development and growth induced by the vascular endothelial growth factor (VEGF) of the endothelial cells, inhibition of the formation of elongated endothelial cells inside collagen 3D gel, with regression due to the induction of apoptosis (Mantell et al.2000).
- Activation of a specific nuclear receptor to inhibit proliferation and promote differentiation of numerous types of tumour cells, and inhibition of the adhesion and migration of cells from the basal membrane, due to a decrease of the expression of integrins alpha-6 and beta-4, which are laminin receptors associated with a greater migration and invasion of prostate cancer cells in vivo (Sung et al.2000).
- Induction of the expression of mRNA of the protein of BRCA1, and of the transcriptional activation by the promotor of BRCA1. The sensitivity to the antiproliferative effects of Vit. D_3 is, in fact, closely connected with the ability to modulate the protein of BRCA1 by transcriptional activation of the factors induced by VDR (Campbell et al. 2000)
- In addition to the antiproliferative effect of VDR, its activation increases the expression of the protein binding the insulin-like growth factor (IGF) (Chokkalingam et al. 2001).
- Increases the expression of the IGF binding protein 3 (IGFBP3), whose presence is indispensable in activating the antiproliferative effect of D_3. Both D_3 and IGFBP3 activate the cyclin-dependent kinase-inhibiting protein p21/WAF 1, which mediates their antiproliferative effect (Boyle et al. 2001).
- Inhibits the signalling of the growth factors of the keratinocytes and induces apoptosis in human prostate cancer cells, induces a reduction of the basal expression of bcl 2, with relative effect (Crescioli et al. 2006).
- Reduces the growth stimulating effect of DHT, and increases the expression of VDR (Ahnonen et al. 2000).
- Influences the gap junctional intercellular communication (GJIC) and during carcinogenesis increases the function of GJIC of the HRPTC (Fujioka et al. 2000).
- Induces the phenotypical transformation of the tumour cells to mature differentiated, physiologically normal cells, at the same time inhibiting neoplastic cell proliferation, reinforcing the antiproliferative effect of Trans-retinoic acid (Barroga et al. 2000).
- Inhibits the invasion of the extracellular matrix (ECM) and metastases by blocking the degradation of the ECM barriers by the tumour calls through collagenolysis (Yudoh et al. 1999).
- Irreversibly inhibits the growth of neoplastic cellular mitosis, blocking it in the G0-G1 phase, with strong inhibition of cloning-proliferation and invasion of the cells (Hisatake et al. 2001).
- Causes an accumulation of cells in the G0-G1 phase, and subsequent apoptosis (Blutt et al. 2000).
- Inhibits tumoural angiogenesis and has antiproliferative, prodifferentiating and proapoptotic effects, greatly reinforced by synergism with the retinoids (Majewski et al. 1994).
- Blocks the tumour cell cycle in the G1 phase, preventing cell proliferation and depleting the concentrations of cyclin C and D1, known activators of cell reproduction (Verlinden et al. 2000).
- Selectively promotes the expression of ICAM-3 adhesion molecules, in a time- and dose-dependent way (Babina et al. 2000).
- Inhibits the expression of the anti-apoptotic protein, Bcl-2, thus favouring apoptosis (Larsen et al. 2001).
- Induces apoptosis, through involvement of the cytosolic phospholipase a2, inducing DNA fragmentation and loss of tumour cell vitality (Pirianov et al. 1999).
- Reinforces the response of the tumour cells to TNF-alpha (Pirianov et al. 1999).
- Disactivates the antiapoptotic effect of broad spectrum caspase inhibitor Z-VAD-FMK (Pirianov et al. 2001).

- Activates another caspase-independent apoptotic pathway, by involvement of ceramide and phospolipase A-2 (cPLA2) (Pirianov et al. 1999).
- Has an antiproliferative effect through induction of the gene amphiregulin and an increase of its mRNA. It thus inhibits EGF, on which amphiregulin acts (Akutsu et al. 2001).
- Expresses an antimitotic effect directly proportional to the concentration of 1 alpha OH-ase and inversely to that of 24OH-ase (Bareis et al. 2001).
- Induces E-cadherin and other adhesion molecules, with a proapoptotic effect (Palmer et al. 2001).
- Significantly inhibits hepatic peroxidation of cytosolic lipids and protects the cellular membranes from free radicals. Has a strong protective effect on the normal cell architecture of hepatocytes and maintains the concentration of the hepatic cytochrome P 450 at physiological levels (Basak et al. 2001).
- Has a strong antiproliferative and prodifferentiating action, also through non-receptorial mechanisms (Consolini et al. 2001).
- Has antiproliferative effects synergically reinforced by retinoic acid with depletion of the levels of the c-myc protein (Stio et al. 2001).
- Induces a greater nuclear expression of the cyclin-dependent kinase inhibitor P27 (kip^1) (Liu et al. 2002).
- Induces a high expression of P21 and P27, cell cycle regulators (Johnson CS 2006).
- Increases the expression of p27, encoder of the cyclin-dependent kinase inhibitors and of gadd4 alpha, growth-arrest and DNA-damage-inducible gene (Prudencio et al. 2001).
- Blocks the expression of the EGF receptor through inhibition of its phosphorylation, with dephospohorylation of polypeptides 17 and 66-kDa, EGF receptors (Lee et al. 2001).
- Reduces the presence of CD34(+) cells with immunostimulating effect (Lathers et al. 2001).
- Promotes the cleavage of the molecule that signals the promotion of mitogen-activated survival and growth (protein Kinase) with caspase-dependent mechanism. Apoptosis occurs through caspase-dependent selective cleavage of MEK-1 and is mediated by p38 MAPK (Mc Guire et al. 2001).
- Depletes the concentration of cyclin C and D1, known activators of cell reproduction (Verlinden et al. 2000).
- Promotes the expression of ICAM 3 adhesion molecules, and acts on leukemia mastocides (Babina et al. 2000).

Vitamin C

- Ascorbic acid is one of the most important reducing agents present in living tissue and is a strong antioxidant, reacting directly with single oxygen atoms, hydroxides and superoxide radicals (Sauberlich 1994).
- Normal human lymphocytes have the ability to concentrate Vit. C intracellularly, helping to protect these cells from oxidative damage (Levine et al. 1996; Ozturk et al. 2001).
- Prevents the cell damage produced by oxidative processes, including free radicals (Padh 1991)
- A statistically significant inverse correlation has been documented between the ingested amounts of Vit. C, carotenes, fruit and vegetables and the incidence of non-Hodgkin's lymphoma (Ward et al. 1994).
- Can have a preventive and therapeutic role in cancer (Bendich and Langseth 1995).
- Inhibits the carcinogenic effects produced by mutagenic substances (Aidoo et al. 1994; Lee et al. 2002).
- Preserves the integrity of connective tissue with antiblastic function (Bendich and Langseth 1995).
- Angiostatic activity on endothelial cell proliferation (Ashino et al. 2003).
- Non-Hodgkin's lymphoma T cells are sensitive to Vit. C. Concentrations of less than 50 micromol/l kill the cells in a few hours (Helgestad et al. 1990).
- Cell lines of lymphoblastic tumours are inhibited by Vit. C (Kao et al. 1993).
- Antineoplastic activity with various mechanisms of action (Cameron et al. 1979; Head 1998).
- Antimetastatic activity by means of collagen synthesis (Pinnel et al. 1987; Peterkofsky 1991)
- Antimetastatic activity through inhibition of hyaluronidase (Cameron et al. 1973).
- Antimetastatic activity by reducing the permeability of endothelial cells to the tumour cell populations (Utoguchi et al. 1995).
- Improves the performance status in tumour patients (Head 1998).
- Increases survival in terminal cancer patients (Cameron et al. 1974; Cameron et al. 1976; Cameron et al. 1978; Cameron 1991).
- Reinforces the efficacy of antitumour drugs in lymphoma cells (Michel et al. 2003; Nagy et al. 2003; Lee et al. 1994; Prasad et al. 1994; Kurbacher et al. 1996; Nagy et al. 2003; Prasad et al. 1992; Sarna et al.1993).
- Reduces the toxicity of chemotherapy drugs such as adriamycin (Fujita et al. 1982; Shimpo et al. 1991)

Bromocriptine and/or Cabergoline

Inhibitors of prolactin, which has the following documented mitogenic activities:

- Strong mitogenic induction (Ben-Jonathan et al. 2002).
- Increases the aggressiveness of colorectal cancers (Bhatavdekar et al. 1994; Bhatavdekar et al. 1995)
- Induces the proliferation of various lines of human breast cancer (Vonderhaar 1998; Vonderhaar 1999)
- Stimulates the proliferation of prostate cancer cells (Janssen et al. 1996)
- Activates the proliferation of acute myeloid leukemia cells (Nishiguchi et al. 1993)

- Positively regulates the proliferation of acute lymphoid leukemia cells (Matera et al. 1997)
- Increases the proliferation of malignant B lymphocytes (Walker et al. 1994)
- Raises the proliferative index of lymphoma cells (Gout et al.1980; Yu-Lee 1990)
- In malignant cells of the immune system, inhibits the apoptotic process (Krumenacker et al. 1998; Buckley and Buckley 2000).
- The prolactin receptor is expressed by most immune system cells (O'Neal et al.1991; Dardenne et al. 1994; Matera et al. 2000)
- Favours the process of hepatocarcinogenesis (Buckley et al. 1988)
- Leiomyomas produce more prolactin than normal myometrium, having a mitogenic action through the locally produced prolactin (Nowak et al. 1993).
- Autocrine/paracrine action of prolactin in the hemopoietic cells (Matera 1996; Ben-Jonathan et al. 2002).
- The prolactin receptor is expressed by most malignant immune system cells (O'Neal et al. 1991; Dardenne et al. 1994; Matera et al. 2000)
- The malignant hemopoietic cells can produce prolactin. It has been reported that myeloid leukemia cells and myeloblasts isolated from patients with acute leukemia produce prolactin (Kooijman et al. 2000).
- Various cell lines of non-Hodgkin's lymphoma produce prolactin (Matera et al. 2000).
- The rat lymphoma cell line, Nb2, depends on prolactin for growth (Davis et al. 1988; LaVoie et al.1995; Ganguli et al. 1996; Camarillo et al. 1997; Camarillo et al. 1998; Krumenacker et al. 1998; Al-Sakkaf et al. 2000; Yu et al. 2000).
- **Participates in the development and/or progression of blood tumours** (Hooghe et al. 1998).

AIMS OF THE DBM

The DBM has 3 main objectives:

a. **Defence** against neoplastic aggression
b. **Inhibition of neoplastic proliferation**
c. **Contrasting the marked mutagenic tendency** of the neoplastic phenotype.

DEFENCE

The DBM supports and enhances vital reactions and antitumoural homeostasis to allow them to counter the onset and progression of a tumour.

The tumour is a deviation from normal life, making it necessary to restore the altered reactions back to normal by reinforcing all the means that Physiology considers essential for life (Di Bella et al. , 1969; Di Bella et al. ,1971; Di Bella et al. 1974; Di Bella et al.1976; Di Bella et al. 1977; Di Bella et al. 1979; Di Bella et al. 1980; Di Bella et al. 1981; Di Bella et al. 1984; Di Bella et al. 1985; Di Bella et al. 1986; Di Bella et al. 1987; Di Bella et al. 1988; Di Bella et al. 1994; Di Bella 1997; Di Bella et al. 1998; Di Bella et al. 2002; Di Bella et al. 2006).

The DBM achieves this objective by means of innovative formulations and criteria for the use of MLT (complexed with Adenosine and Glycin), of retinoids solubilized in Vit. E, together with Vitamins C, D_3, and components of the ECM. Including apolar components such as Betacarotene and vit. E among the phospholipids of a cellular membrane stabilizes it and preserves it from oxidative damage and free radicals (Shklar et al. 1996; Israel et al. 2000; Khuri et al. 2001; Di Bella , 2005; Dong et al. 2008; Lubin et al. 2008; Nesaretnam et al. 2008; Watters et al. 2009).

Both in situations that predispose to tumours and in actual neoplastic diseases, the structure and potential of the cellular membrane and, consequently, its expression and receptor functions, can be altered by deterioration of the oxidative processes and a consequent peak of free radicals. The doses foreseen by the DBM of retinoids and vit. E make it possible to achieve both a preventive and therapeutic effect, cancelling the possibility of damage caused by the free radicals (Odeleye et al. 1992; Launoy et al. 1998; Shimizu et al. 2004; Di Bella, 2005; Elangovan et al. 2008; Neuzil et al. 2002; Frei et al. 2008).

The aim of optimizing vital reactions and defending them against neoplastic aggression is achieved with:

- **Retinoids** (Kapil et al. 1993; Lotan et al. 1997; Muller et al. 1997; Roth et al. 1999; Khuri et al. 2001; Hashimoto et al. 2003; Di Bella G. 2005; Barroga et al. 2000; Dong et al. 2008; Bonofiglio et al. 2009);
- **Vit. E** (Israel et al. 2000; Jatoi et al. 2002; Neuzil et al. 2002; Di Bella, 2005; Lubin et al. 2008; Elangovan et al. 2008; Nesaretnam et al. 2008);
- **Vit. D_3** (Meggouh et al. 1990; Di Bella, 2005; Giovannucci et al. 2006; Amir et al. 2009; Chiang et al. 2009; Chung et al. 2009; Reicharth et al. 2009; Schwartz et al. 2009; Fernandez et al. 2009; Goodwin et al. 2009);
- **Vit. C** (Cameron et al. 1979; Murata et al. 1982; Di Bella, 2005; Frei et al. 2008; Ha et al. 2009)
- **MLT** (Di Bella et al. 1971; Di Bella et al. 1974; Di Bella et al.1976; Di Bella et al. 1977; Di Bella et al. 1979; Di Bella et al. 1980; Di Bella et al. 1981; Di Bella et al. 1984; Kvetnoĭ et al. 1986; Di Bella et al. 1988; Maestroni et al. 1996; Di Bella et al. 1997; Di Bella et al. 1998; Cos et al. 2000; Bartsch et al. 2001; Di Bella et al. 2002; Di Bella 2005; Di Bella et al. 2006; Joo et al. 2009; Di Bella et al. 2009; Grant et al. 2009; Di Bella et al. 2009; Di Bella et al. 2009)
- **Components of the Extracellular Matrix (ECM)** (Batra et al. 1997; Kidd et al. 2000; Mikami et al. 2001; Di Bella 2005; Asimakopoulou et al. 2008; Yamada et al. 2008).

Retinoids and Melatonin have the ability to preserve and enhance the trophism, vitality and efficiency of healthy cells, at the same time depressing the progression, vitality and marked mutagenic tendency of the neoplastic phenotype (Di Bella et al. 1979; Di Bella et al. 1997; Onogi et al. 1998; Mediavilla et al. 1999; Bartsch et al. 1999; Wang et al. 1999; Khuri et al. 2001; Di Bella 2005; Di Bella et al. 2006; Garcia-Santos et al. 2006; Bogos et al. 2008; Martín-Renedo et al. 2008; Yap et al. 2008; Watters et al. 2009; Williams et al. 2009; Wu et al. 2009; Ginestier et al. 2009; Di Bella et al. 2009; Yin et al. 2009; Kim et al. 2009; Di Bella et al. 2009).

This apparent contradiction is based on the fact that retinoids are the most potent non-hormonal activators *only* of ordered, structural and functional growth for specific optimum biological equilibrium, while they decidedly inhibit disordered and non-specific neoplastic growth, causing apoptosis of the tumour cells.

Vitamins, on the other hand, are physiological catalysts between energy and matter.

Any change to living matter cannot exclude an adaptation of the energy status. Only slight variations in production quantity and absorption, i.e. the processing of the biological matter and its energy counterpart, are compatible with life: the reactions must take place gradually with minimal matter-energy variations, compensating each other over time. These reactions very gradually cause the production and absorption of energy and matter with material-energy equivalence. This continuous process, due to its exceptional purposes, must be gradually modulated and finely regulated, and would be impossible without vitamins, whose purpose is the conditioning and regulation of the matter-energy equilibrium on which life depends.(Di Bella 2005).

Complete knowledge of vitamins is the equivalent of knowledge of the most subtle energy-matter equilibriums and relationships and of all the reflections on life's activities. Knowing the chemical composition, the formation, and the localisation of vitamins within a cell, the time of their intervention, the regulation and extent of their activity makes it possible to understand the essence of physiological life and to correct its pathological deviation. From their original biochemical-vital role, the rationale of vitamins in the DBM has risen to a therapeutic level that is essential both in preventing and curing various diseases. An in-depth knowledge of the regulatory mechanisms of normal physiological life thus makes it possible to devise effective countermeasures aimed at preventing degenerative or neoplastic deviations (Di Bella 2005). ***Figure 1.***

To understand the enormous importance of retinoids in biological economy, it is sufficient to consider that they provide the high energy cost both for growth and for the physiological order of growth, contributing to antitumoural homeostasis. The growth of living substance involves very high expenditure of energy, but physiological control of growth involves an equally high requirement of energy.

INHIBITION OF NEOPLASTIC PROLIFERATION

The ubiquitary receptorial expression of prolactin and GH (De Souza et al. l974; Di Bella et al. 1979; Di Bella et al. 1981; Di Bella et al. 1997; Hooghe et al. 1998; Di Bella et al. 1998; Ben-Jonathan et al. 2002; Di Bella 2005; Di Bella 2009) represents one of the aspects of the direct and generalised mitogenic role of these molecules.

Cellular proliferation is strictly dependent on prolactin (Bonneterre et al. 1990; Di Bella et al. 1997; Di Bella et al. 1998;Tada et al. 1999; Gruszka et al. 2001; Di Bella 2005; Florio et al. 2008; Mouton 2008; Di

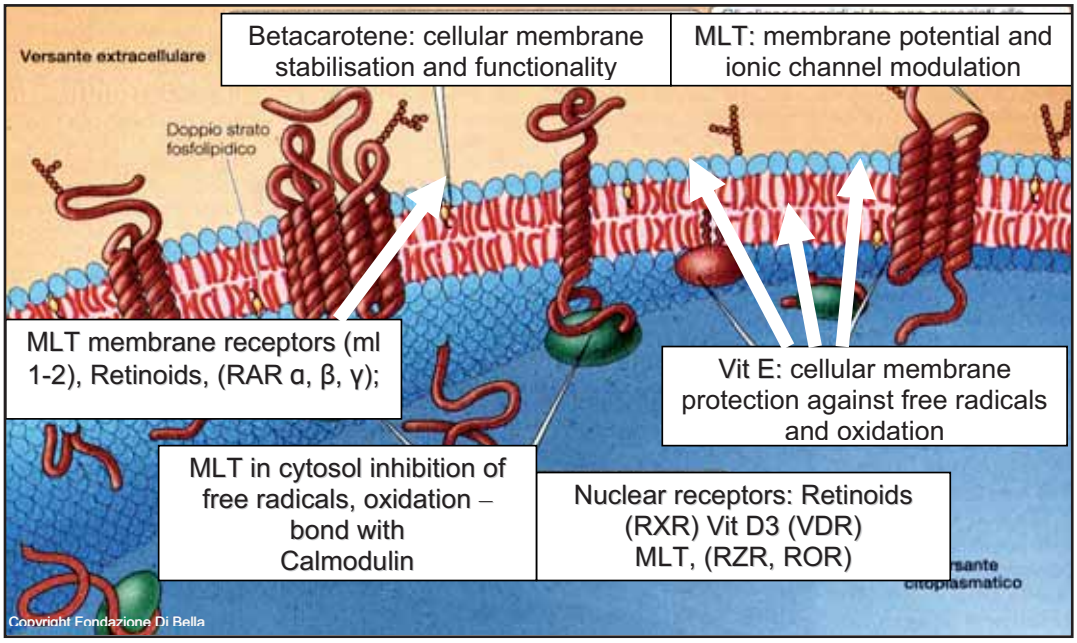


Figure 1. The cellular membrane (in blue, containing the phospholipids layer in red) is a defence, a vital filter through which everything passes, from inside the cell outwards, where the stimuli and the conditionings are absorbed and analysed from the outside towards the inside and vice versa, communication takes place and impulses and signals are emitted and received. Optimising this process and making it efficient means making the cell capable of defending itself in optimum conditions: Vit. E and Betacarotene protect and stabilise the membrane, while MLT physiologically modulates its potentials, regulating the ionic channels and the entire receptorial dynamics and expression.

Bella 2009), on GH, the most important growth factor (De Souza et al. l974; Di Bella et al. 1979; Di Bella et al. 1997; Di Bella L et al. 1998; Lincoln et al. 1998; Friend et al. 2000; Barnett et al. 2003; Anthony et al. 2009), and on GH-dependent mitogenic molecules positively regulated by GH, such as EGF, FGF, HGF, IGF1-2, NGF, PDGF, TGF, and VEGF (Szepesházi et al. 1999; Murray et al. 2004; Sall et al. 2004; Di Bella 2009; Hagemeister et al. 2008; Di Bella et al. 2009; Taslipinar et al. 2009), as well as on growth factors produced by the gastrointestinal system, such as VIP, CCK, and PG (Kath et al. 2000).

Both physiological and neoplastic cellular proliferation is triggered by these same molecules, which the neoplastic cell thus uses exponentially compared with a healthy cell. The loss of differentiation and uncontrolled proliferation, albeit to different extents, characterise all tumours.

The use of somatostatin and its analogues, by acting on growth, the common denominator of every tumour, must be based on a rational indication in every tumour (Di Bella et al. 1979; Di Bella et al. 1981; Di Bella et al. 1997; Pollak et al. 1997; Di Bella et al. 1998; Pawlikowski et al. 1998; Friend et al. 2000; Lachowicz et al. 2000; Friend et al. 2000; Schally et al. 2001; Massa et al. 2004; Di Bella 2005; Arena et al. 2007; Guillermet-Guibert et al. 2007; Di Bella 2008; Lee et al. 2008; Verhoef et al. 2008; Vieira Neto et al. 2008; Volante et al. 2008; Ben-Shlomo et al. 2009; Di Bella et al. 2009 ; Bellyei et al. 2010).

In many tumours, not just neuroendocrine types, a receptorial expression for somatostatin has been documented (Moertel et al. 1994; Sestini et al. 1996; Kogner et al. 1997; Briganti et al. 1997; Van Eijck et al. 1998; Borgström et al. 1999; Friend et al. 2000; Albérini et al. 2000; Florio et al. 2000; Cattaneo et al. 2000; Steták et al. 2001; Orlando et al. 2001; Faggiano et al. 2008; Florio et al. 2008; Fusco et al. 2008; Kwekkeboom et al. 2008; Hubalewska-Dydejczyk et al. 2008; Ioannou et al. 2008; Khanna et al. 2008; Li et al. 2008; Corleto et al. 2009; Edelman et al. 2009; Hassaneen et al. 2009; He et al. 2009; Laklai et al. 2009; Luboldt et al. 2009; Pisarek et al. 2009; Ruscica et al. 2010).

The causal relationship between the receptorial expression of GH (of which SST is the biological antidote) and tumoural induction and progression has been demonstrated (Friend et al. 2000; Zeitler et al. 2000; Gruszka et al. 2001), showing much higher histochemical concentrations of GHR in tumoural tissues with respect to healthy tissue. The powerful mitogenic role of GH is therefore known and amply documented, as is the fact that the proliferative index and the speed at which the tumour populations progress are directly proportional to the receptorial expression of GH (Lincoln et al. 1998). ***Figure 2.***

The inhibition of various oncogenes, including MIC, by SST and the other components of the DBM has been reported (Degli Uberti et al. 1991; Peverali et al. 1996; Sun et al. 2002; Gumireddy et al. 2003; Durand et al. 2008; Aktas et al. 2010).

The known causal factors of oncogenesis also include chromosomal damage, leading, to varying extents, to inactivation of oncosuppressor genes: CD44, Bcl-2, P53, as well as Caspases 3–8, key elements in the apoptotic cascade. The negative regulation of oncosupressors is antagonised by the components of the DBM, such as Retinoic acid, which inhibits the inactivation of the caspases (Piedrafita et al. 1997; Takada et al. 2001; Jiang et al.

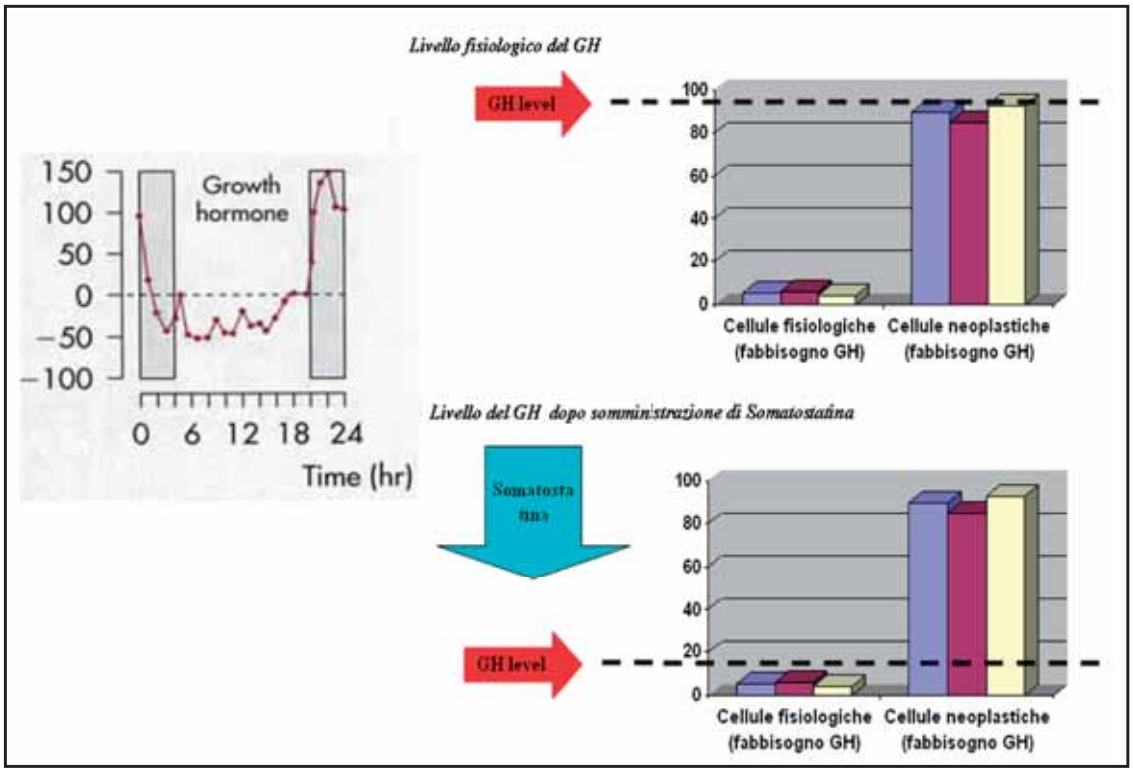


Figure 2. The doses and methods of administration of Somatostatin foreseen by the DBM make it possible to lower the plasma concentrations of circulating GH, while maintaining a sufficient level to ensure the indispensable use by the various physiological districts.

2008) and MLT which preserves P53 and Bcl-2 from degradation (Mediavilla et al. 1999). The inactivation of oncosuppressors can take place at the same time as amplification of oncogenes such as the N-myc gene and the proto-oncogene TRK, considered one of the neoplastic cytogenic causes. Components of the DBM such as STT and the retinoids (Giannini et al. 1997; Witzigmann et al. 2008; Quan et al.2008) antagonize the proliferative incentive of these molecules. Among the pathogenetic factors, the alteration of the GF-TRK ligand-receptor system and the altered response to the differential stimulus are effectively countered by the retinoids (Hassan et al. 1990; Giannini et al. 1997; Peverali et al. 1996; Voigt et al. 2000, Kulikov et al. 2007; Huang et al. 2009; Wu et al. 2009; Witzigmann et al. 2008). Differentiation is synergically reinforced by other components of the DBM, such as MLT (Cos et al. 1996; Garcia-Santos et al. 2006; McMillan et al. 1999), Vit D_3 (Lange et al. 2007; Gocek et al. 2009), Vit E (Turley et al. 1995; Swettenham 2005), Vit C (Carosio et al. 2007), and chondroitin sulfate (Batra et al. 1997; Liang et al. 2009). It is known how the GH-IGF1 axis has a determining influence on biological neoplastic development (Murray et al. 2004). The IGFR respond mitogenically to IGF. The suppressive effect of SST and its analogues on serum levels of IGF1 is both direct, through inhibition of the IGF gene (Cascinu et al. 1997), and indirect, by suppression of GH and thus of its hepatic induction of IGF1 (Sall et al. 2004; Murray et al. 2004; Taslipinar et al.2009).

The tumour cells are characterised, albeit to different extents, by various levels of expression of tyrosine kinase receptors. The protein kinase activity is effectively inhibited by SST and its analogues (Reardon et al. 1996; Pawlikowski et al. 1998; Lachowicz-Ochedalska et al. 2000; Cattaneo et al. 2000; Florio et al.2001; Massa et al. 2004; Lee et al. 2008; Florio et al. 2008). The expression of TRK-B and the amplification of N-Myc, together with the high telomerasic activity, common to various tumours, are negatively regulated by SST (Degli Uberti et al. 1991; Sun et al. 2002; Durand et al. 2008). Biological antidotes of GH, such as Somatostatin and its analogues, reduce the expression and transcription of highly mitogenic growth factors, such as IGF 1-2 (Sall et al. 2004), FGF (Held-Feindt et al. 1999), VEGF (Albini et al. 1999; Vidal et al. 2000). The inhibitory activity of SST on another potent mitogenic growth factor, EGF, has also been reported (Watt et al. 2009), acting through multiple mechanisms such as the dose-dependent inhibition of tyrosine phosphorylation induced by the activation of EGFR by EGF (Mishima et al.1999), the reduction of EGFR in tumour cells (Szepesházi et al. 1999), the reduction of the expression of EGF (Held Feind et al.2001), and the depletion of the plasma concentrations of EGF (Cascinu et al.1997;Mishima et al. 1999; Szepesházi et al. 1999; Held-Feindt et al. 1999).

Somatostatin and its analogues extend their negative regulation to the respective receptors with evident antiproliferative and antiangiogenic repercussions (Manni et al. 1989; Barrie et al. 1993; Klijn et al. 1996; Pollak et al. 1997; Pawlikowski et al. 1998; Mishima et al. 1999; Lachowicz-Ochedalska et al. 2000; Friend et al. 2000; Schally et al. 2001; Watson et al. 2001; Schally et al. 2003; Massa et al. 2004; Di Bella 2005; Arena et al. 2007; Guillermet-Guibert et al. 2007; Bocci et al. 2007; Di Bella 2008; Lee. 2008; Di Bella et al.2009).

It is now a confirmed fact that neoplastic progression is strictly dependent on angiogenesis and that this represents an obligatory and essential phase. Acquisition of an angiogenic phenotype is decisive for expansion of the tumour (Longo 2002). Somatostatin and its analogues negatively regulate the "angiogenic inductors" and all the phases of angiogenesis (Jia et al. 2003; Kunert-Radek et al. 2008) such as the cascade of monocytes (Wiedermann et al. 1993), interleukin 8, Prostaglandin E 2 and VIP, endothelial nitric oxide synthase (e-Nos) (Florio et al. 2003) as well as growth factors whose synergism is essential for angiogenesis, such as VEGF-A (Cascinu et al. 2001; Mentlein et al. 2001), TGF, (Murray et al.. 2004; Hagemeister et al. 2008), FGF, HGF (Jia et al.. 2003; Hagemeister et al. 2008), and PDGF (Cattaneo et al. 1999). The inhibition of angiogenesis induced by SST is synergically and factorially reinforced by the other components of the DBM, such as MLT (Lissoni et al. 2001), Retinoids (Majewski et al. 1994; McMillan et al. 1999; Kini et al. 2001; Liu et al. 2005), Vit D_3 (Mantell et al. 2000; Kisker et al. 2003), Vit E (Shklar et al. 1996; Tang et al. 2001), Vit C (Ashino et al. 2003), prolactin inhibitors (Turner et al. 2000), and components of the extracellular matrix (Ozerdem et al. 2004; Liu et al. 2005). The cytostatic, antiproliferative, and antimetastatic effects of Somatostatin have also been documented (Di Bella et al. 1979; Di Bella et al. 1981; Kogner et al. 1997; Di Bella et al. 1997; Schally et al. 1998; Di Bella et al. 1998; Orlando et al. 2001; Schally et al. 2003; Di Bella 2005; Arena et al. 2007; Krysiak et al. 2006; Guillermet-Guibert et al. 2007; Barbieri et al. 2008; Colucci et al. 2008; Di Bella 2008; Gambini et al. 2008; Li et al. 2008; Watt et al. 2008; Shima et al. 2008; Quan et al.2008; Van Keimpema et al.2008 ;Chen et al. 2009; Di Bella et al. 2009; Liu et al.2009; Oberg et al. 2009; Hauser et al. 2009; Jia et al. 2009; Kaprin et al. 2009; Songgang et al. 2009; Nakashima et al. 2009; Zou et al. 2009; Ruscica et al. 2010). These effects are effectively synergised by the other components of the DBM.

Retinoids (Di Bella et al. 1979; Di Bella et al. 1981; Hassan et al. 1990; Di Bella et al. 1997; Onogi et al. 1998; Di Bella et al. 1998; Peverali et al. 1996; Piedrafita et al. 1997; Voigt et al. 2000; Di Bella G. 2005; Witzigmann et al. 2008; Di Bella 2008; Schilling et al. 2008; Pyronnet et al. 2008; Di Bella et al. 2009; Nakagawa et al. 2009),

Melatonin (Di Bella et al. 1979; Di Bella et al. 1981; Kvetnoï et al. 1986; Maestroni et al. 1996; Cos et al. 1996; Di Bella et al. 1997; Di Bella et al. 1998; Bartsch et al. 1999; Mediavilla et al. 1999; Cos et al. 2000; Di Bella 2005; García-Santos et al. 2006; Mc Millan et al.2007; Di Bella 2008; Srinivasan et al. 2008; Bonofiglio et al. 2009; Di Bella et al.2009; Srirajaskanthan et al. 2009),

Vitamin D_3 (Barroga et al. 2000; Campbell et al. 2000; Jensen et al. 2001; Stio et al. 2001; Di Bella G. 2005; Di Bella G. 2008; Gocec et al. 2009; Di Bella G. et al. 2009),

Cabergoline and Bromocriptine (prolactin inhibitors) (Di Bella et al.1979; Di Bella et al.1981; Klijn et al. 1989; Klijn et al. 1996; Di Bella et al. 1997; Di Bella et al. 1998; Lissoni et al.2000; Gruszka et al. 2001; Frontini et al.2004; Di Bella 2005; Senogles et al. 2007; Di Bella 2008; Mouton et al. 2008; Di Bella et al. 2009; Srirajaskanthan et al. 2009),

Galactosamine sulfate, Calcium (Batra et al. 1997; Di Bella 1997; Di Bella et al. 998; Pumphrey et al. 2002; Di Bella 2005, Di Bella 2008; Di Bella et al. 2009),

Vit. E (Cameron et al. 1979; Di Bella et al. 1979; Turley et al. 1995; Shklar et al. 1996; Di Bella et al. 1997; Di Bella et al. 1998; Israel et al. 2000; Malafa et al. 2002; Neuzil et al. 2002; Di Bella 2005; Di Bella 2008; Di Bella et al. 2009),

Vit. C (Murata et al. 1982; Head et al. 1998; Steták et al. 2001; Di Bella 2005; Carosio et al. 2007; Florio et al. 2008, Di Bella 2008; Di Bella et al. 2009).

The literature has therefore confirmed the differentiating antineoplastic and cytostatic, antiproliferative, antiangiogenic and antimetastatic mechanisms of action of all the components of the DBM.

Without the contribution of the growth hormone (GH) and the growth factors (GF) produced by the tissues by GH activity, no physiological or tumoural growth can take place. Cellular mutations are caused by various physical, chemical and infectious agents. Several components of the DBM (MLT, Vit. D_3, C, E, Retinoids, components of the ECM) have a differentiating effect

The growth of hormone-dependent tumours also involves estrogen (tumours of the breast and uterus) and testosterone (prostate and testicular cancer).

GROWTH RECEPTOR MECHANISM

By activating their respective membrane receptors (GHR, GFR and PRLR), the GH, GF and PRL molecules trigger chemical reactions of phosphorylation, transferring the signal from the cellular membrane to the nucleus. The larger the amount of GHR in a tumour cell, the greater its capacity to use the GH, and thus to grow, both locally and also to expand remotely.

The ***dose-dependent relationship between receptor expression of GH in tumour cells and their speed and ability to expand locally and to migrate and produce metastases has been extensively demonstrated.***

Since it has been definitively and scientifically proved that a tumour is a growth, and that this growth depends on GH, GF and PRL, the obvious main therapeutic objective for the cure of any tumour cannot logically exclude the inhibition of GH, GF and PRL by means of Somatostatin and the prolactin inhibitors Cabergoline and/or Bromocriptine. The inhibition of tumour growth by blocking the growth hormone through its biological antidote, Somatostatin (SST), thus follows a simple, linear, understandable and mathematical logic. ***Figure 3.***

The same concept and the same therapeutic rationale apply to the pharmacological blocking of prolactin by means of the relative inhibitors, such as Bromocriptine and Cabergoline. The same concept and the same therapeutic rationale apply in oncology to the blocking of estrogens and androgens in the respective hormone-dependent tumours. But oncology still does not understand the need to extend the same concept to the inhibition of the most potent ubiquitary oncogenes: GH, (GH-dependent) GF and PRL.

Oncology continues to play about with the somatostatin receptor (SSTR), limiting its use to situations in which the receptor is identified in the tumour cells.

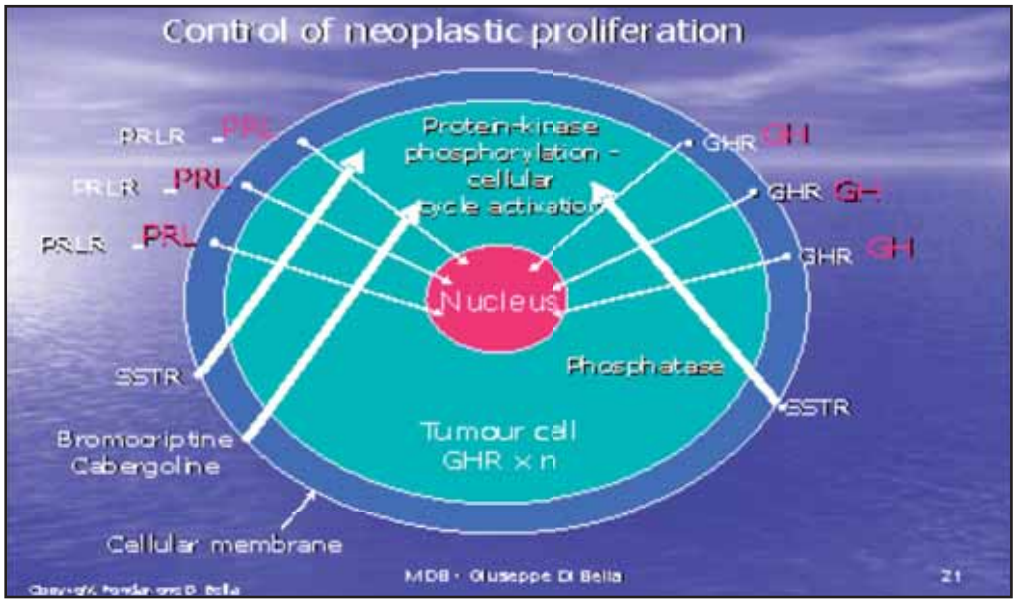


Figure 3. The growth hormone GH is in direct contact with the respective receptor GHR, at the level of the cellular membrane (in blue). The contact triggers transduction and amplification of the signal to the nucleus (in red). The reactions are **protein-tyrosine kinase phosphorylation events**. These reactions are blocked by somatostatin (SST) which, by activating its receptor SSTR, triggers OPPOSING enzymatic **phosphatase** systems **which disactivate** the protein-tyrosine kinase phosphorylation chain, inhibiting the neoplastic proliferation. This direct antitumoural action of SST on the tumour cell is combined with its equally potent indirect action, consisting of the reduction of the blood concentrations of GH and consequently of GF.

The test generally carried out for this search is Octreoscan. This test consists of an intravenous injection of a radiolabelled somatostatin analogue, usually Octreotide, and scintigraphy to detect the presence of SSTR in the tissues. This technique is not particularly reliable as it is not always capable of identifying even two of the seven receptors of somatostatin, numbers 2 and 5, and has proved to give a high percentage of false negatives. More reliable procedures, such as immunohistochemistry and reverse transcriptase, have in fact ascertained the presence of SSTR in many situations which gave completely negative results with Octreoscan (Schaer et al. 1997; Van Eijck et al. 1998; Held-Feindt et al. 1999; Mishima et al. 1999; Pinzani et al. 2001; Watson et al. 2001; Barnett et al. 2003). The conviction that Octreoscan helps in ascertaining the usefulness of somatostatin is therefore obsolete. Octreoscan has no effect whatsoever on the rationale of treatment with somatostatin for a number of reasons: all tumour cells have dose-dependent growth indices relative to the expression of the growth hormone receptor (GHR) inhibited by somatostatin (Lincoln *et al.* 1998). GH also promotes tumour growth by means of an indirect mechanism: induction of "**Growth factors" (GF)**, highly mitogenic molecules which can be produced by tissues if activated by GH.

In the absence of growth hormone (GH), no tissue can produce **Growth factors.**
GH thus has an essential, powerful and dual mitogenic role:

- ***directly*** on the growth of the tumour cells, by activation of the respective receptors (GHR),
- ***indirectly*** through induction in the tissues of growth factors, which in turn represent a powerful acceleration of neoplastic growth. ***Figure 4.***

Using somatostatin to negatively regulate GH and GH-dependent GF thus acts directly on tumour growth, regardless of whether somatostatin receptors (SSTR) are present or not in the tumour cells. The presence of SSTR on the membrane of the tumour cell can accelerate or intensify the response to SST, but this response would in any case occur for the reasons stated above.

The concept of restricting the use of somatostatin to the detection of one of its receptors in the tumour is therefore irrational. In addition, even when somatostatin receptors are not found in the tumour, they are in any case always present in the vessels around the tumour.

By blocking GH and the relative GF, SST is thus the most powerful inhibitor of tumoural proliferation and represents a necessary and essential component, albeit not sufficient, in the treatment of all tumours, with or without the presence of somatostatin receptors, and limiting, therefore, the therapeutic indications for using monoclonal antibodies. Monoclonal antibodies inhibit the kinases activated by the GF, but it has been extensively documented *that SST inhibits the gene expression of all the GF, blocks their transcription and extends the block to the expression and transcription of their respective receptors.* By reducing the rate of circulating GH with SST, the basic molecule necessary for the synthesis

Figure 4. The GH-dependent growth factors that carry out a leading role in neoplastic induction and progression include epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), IGF 1-2 produced by the liver, nerve growth factor (NGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and transforming growth factor (TGF), etc…

of GF is already eliminated. The toxicity of monoclonal antibodies is due to the fact that the receptor of the cellular membrane on which the monoclonal antibody acts does not consist only of the GF gene to be blocked, but of an entire family of genes all inactivated by the monoclonal antibody. It is precisely this unwanted but unavoidable blocking of all the other genes connected to the GF receptor that causes toxicity. Monoclonal antibodies are often used together with or following chemotherapy, with a logic that is difficult to understand: chemotherapy is in fact cytotoxic and cytolytic, it eliminates and/or intoxicates the cells, but in the large percentage of cells that it does not eliminate it destroys to a greater or lesser extent the more exposed fragile surface layer of the cell, the cellular membrane, the site of the receptors on which the monoclonal antibodies act, thus eliminating or destroying the receptor sites on which the MA should act, or severely denaturing membrane potentials, the ionic channels and the transduction chain of the signal to the nucleus. It is as if a switch were put out of action or the wire connecting the switch to a bulb were cut and one still expected the light to work. ***Figure 5.***

The blood vessels around the tumour do in fact present a constant concentration of **SSTR** which, if activated by somatostatin, negatively regulate angiogenesis, and consequently the progression of the tumour. It has in fact been documented that even in cases in which no SSTR is detected in the tumour, somatostatin acts directly and effectively, blocking the growth of the tumour through inhibition of angiogenesis, and without angiogenesis no tumour can develop. In the cells of Kaposi's sarcoma, in which SSTR were found to be totally absent, growth was completely blocked by somatostatin. The blood vessels around Kaposi's sarcoma, however, have been shown to contain a high density of SSTR, and the cytostatic effect of SST is therefore a result of the antiangiogenic effect (Albini, et al. 1999).

Until the cells that form the first tumoural aggregate measuring just a few millimetres are able to create their own system of blood vessels (***neoplastic angiogenesis***), they grow very slowly and remain at the "carcinoma in situ" stage. Expansion of the tumour only takes place when ***angiogenesis*** occurs, i.e. when the tumour succeeds in creating a network of blood vessels to ensure the supply of nutritional substances and eliminate metabolic waste. The literature has shown that ***all the stages of angiogenesis are negatively regulated by somatostatin and its analogues and, albeit to a lesser extent, by all the other components of the DBMS.*** If angiogenesis is an obligatory phase of neoplastic expansion and if angiogenesis is totally inhibited by somatostatin, then its indication in all tumours, regardless of the presence of SSTR, is additionally supported.

Even local situations of anoxia and acidosis favour angiogenesis and can often be corrected by the improvement of the blood-tissue exchanges induced by the differentiating components of the DBM. ***Figure 6.***

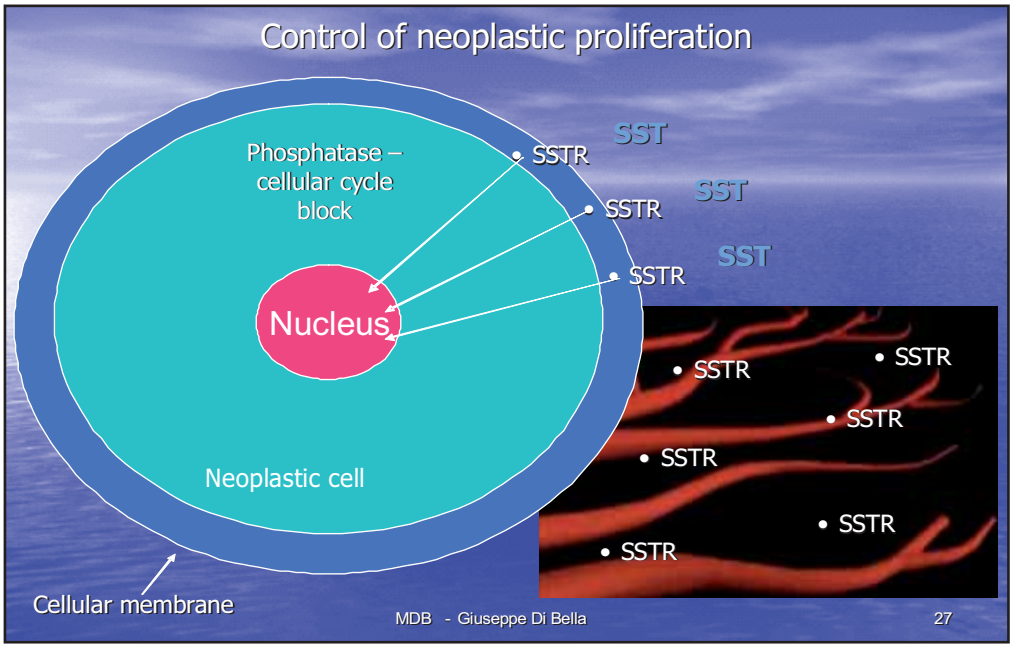


Figure 5. Blue indicates the cellular membrane with the somatostatin receptors (SSTR), while green represents the cytoplasm of the cell inside the membrane, in which the chemical reactions activated by the contact between SST (ligand) and the SSTR take place. These reactions **(phosphatase),** indicated with the white arrows, **block the protein-tyrosine kinase phosphorylation reactions of the tumoural proliferation** induced by GH and GF. On the right side of the figure is a schematic representation of the blood vessels surrounding the tumour and giving it nutritional support with a high and constant expression of SSTR.

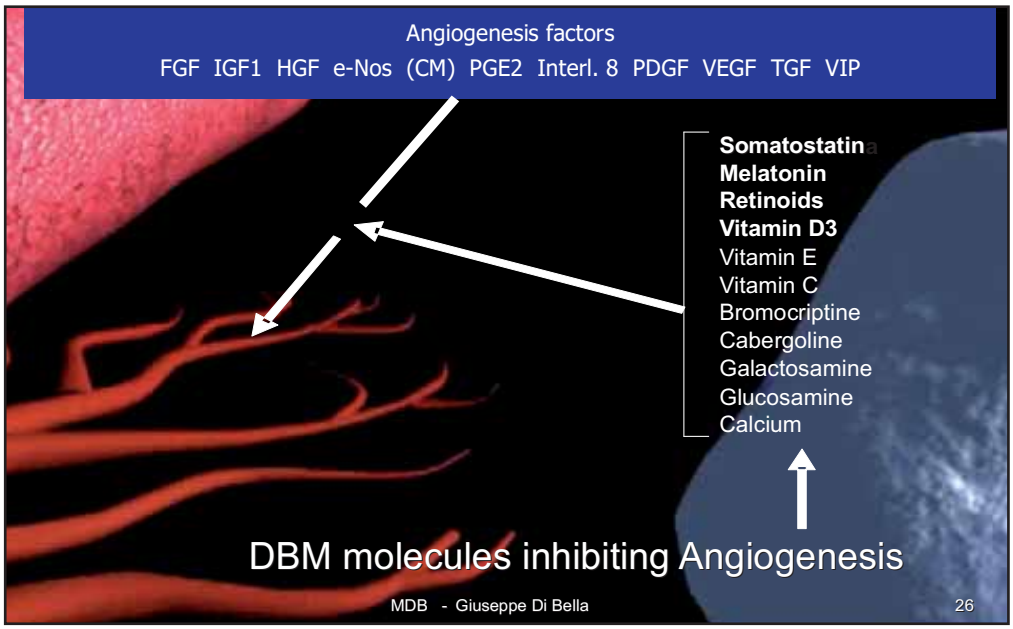


Figure 6. Molecules which contribute to the promotion of angiogenesis and synergically inhibited by somatostatin and every other component of the DBM:
Endothelial nitric oxide synthase (eNOS), Interleukin 8 (Il8), GH-induced monocyte chemotaxis (MC), Prostaglandin 2 (PG2), Fibroblast growth factor (FGF), Hepatocyte growth factor (HGF), Hepatic-derived insulin growth factor (IGF 1-2), Platelet-derived growth factor (PDGF), Vascular endothelial growth factor (VEGF), Transformation growth factor (TGF)

CONTRASTING THE MUTAGENIC TENDENCY OF THE NEOPLASTIC PHENOTYPE

Inhibition of the tumour cell mutations

The other fundamental aspect of neoplastic progression, and thus an objective of the therapeutic rationale of the DBM, consists of the tumour cell mutations. With every mutation, the cell selects and acquires a series of advantages. Differentiating properties of DBM components, such as Melatonin, Retinoids, VIT E, C, D_3, and components of the extracellular matrix (ECM), contrast the marked mutagenic tendency of the neoplastic phenotype. ***Figure 7.***

The strategic objectives of an antiblastic treatment cannot, therefore, exclude control of the mutations, which represent an essential feature and a common denominator of tumour cells, not least because of their dependence for growth on GH, PRL, and GF.

Tumour cells are characterised by an increasing frequency of mutations, followed by a predefined programme of survival inherited from bacteria (Radman *et al.* 1975) (transferred from prokaryotes) defined by Radman as the "SOS" system, which is repressed in healthy cells and accessed in conditions of acute stress.

This survival programme triggers a predefined process that allows the cell that has become neoplastic to adapt very rapidly and efficiently to the adverse conditions, with a modulated progression by means of a predetermined development mechanism.

The model which continues to dominate the official standards of oncology has still not assimilated this essential aspect of neoplastic evolution, a necessary stage in understanding oncological biology and interpreting the evolutionary processes involved in the progression of tumour diseases (not to be confused with a Darwinian concept). The protagonists of this development are in fact natural selection and genetic variation. Natural selection acts on genetic variation by providing evolutional advantages to phenotypes and genotypes which have adapted best to the environment.

The source of the genetic diversity is the mutation in the DNA sequences, and the mutation is a phenomenon, by definition, which is totally casual, managed totally by chance.

Within the framework of evolution, in which mutations and natural selection occur, it is thus clear that everything is guided by chance.

Cancer also follows this evolutional path and it is certainly a somatic process totally guided by chance that leads to carcinogenesis. In man this is a genetic process, the dynamics being regulated by the interaction between mutation, selection and the mechanisms of antiblastic homeostasis of tissue organisation, a process specific and obviously limited to higher multicellular complex organisms. The evolution of a cell towards malignancy starts with one or more casual mutations.These mutations obviously provide the cell

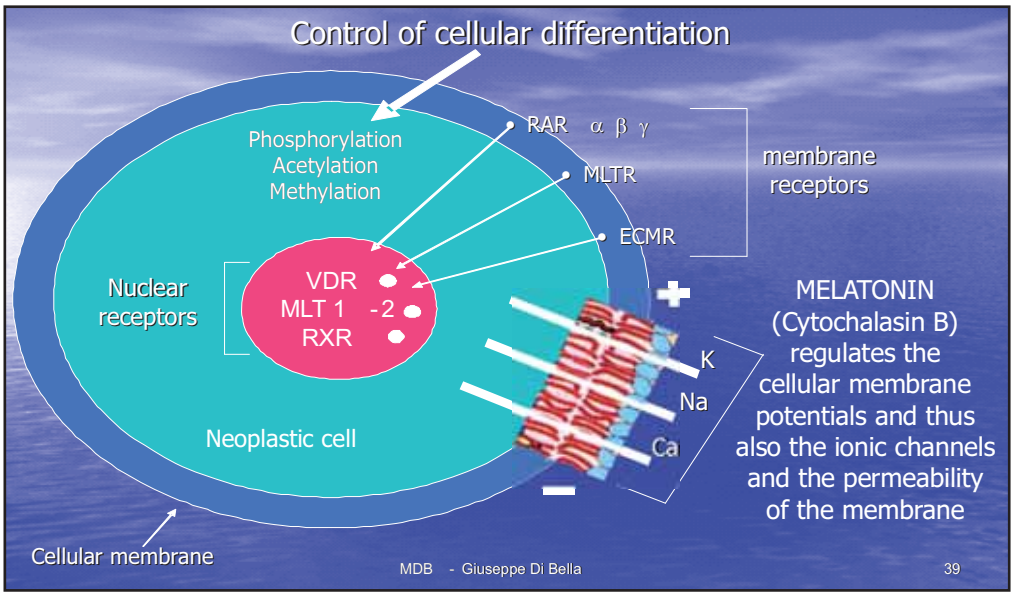


Figure 7. The differentiating receptor sites are indicated on the blue cellular membrane: **RAR** the retinoic acid receptors, with 3 subgroups (**alpha, beta and gamma), MELR** the melatonin receptor, **ECMR** the extracellular matrix receptor. In the nucleus, in red, are the nuclear receptors: **RXR** the retinoic acid receptor, **VDR** the vitamin D3 receptor, **ROR and RZR alpha and beta** the Melatonin receptors. The ligands of these receptors, both membrane and nuclear, **are components of the DBM, and combine a differentiating synergic response with the antiproliferative reinforcement of SST and prolactin inhibitors.** If activated promptly and synergically, all these receptor blockades of the tumour mutations and proliferations **are difficult to overcome**. In the enlarged membrane area with the + and – signs above and below, **are the ionic channels of calcium, sodium and potassium, vitally important for biological equilibrium and to contrast the tumour: modulated by melatonin by controlling the membrane potentials, they carry out their differentiating effect by activating reactions of Phosphorylation, Methylation and Acetylation.**

with an advantage in proliferative terms and are thus in some way used by the selection. A tumoural disease is therefore currently interpreted as being evolutional. The accumulation of mutations will naturally produce subsequent waves of clonal expansion.

According to the prevailing model of the orthodox vision of cancer, it is a genetic disease, originating above all from the mutation of 2 classes of genes, oncogenes and oncosuppressors, thus from mutations of genes that regulate differentiation and growth, and directly involved in evolution, and of those in charge of maintaining the integrity of the DNA, ensuring the constancy of DNA synthesis and its repair by means of the many mechanisms that have appeared during evolution. Among the genes that regulate antiblastic homeostasis, a fundamental role is played by those that generate apoptosis. Every time one or more mutations occur in these genes, the tumour disease progresses. When a mutation occurs in the DNA damage repair genes, then what has been defined as genetic instability takes place, i.e. the mutant phenotype. A simple mutation of a healthy cell would not be able to explain this accumulation of mutations and thus the presence of a much more unstable phenotype is called for.

There is probably a positioning error as regards the concept of genetic instability. According to Radman's theory (based on a survival system named *SOS* and supported by professor Israel and Italian authors), two fundamental players are the LexA gene and the RecA gene, together with the relative proteins.

The LexA gene is a transcriptional repressor, while the RecA gene is a positive regulator. The relative publications should be referred to for more details.

In conditions of stability, the "*SOS*" survival programme is not active but is repressed by the Lex A gene. The "*SOS*" system consists of around twenty genes and when the DNA is damaged or the survival of the cell is in danger, the Lex A protein is somehow inactivated by the production of another protein, Rec A, and at this point the genes are activated. This system is undoubtedly triggered by casual mutations, favourably selected and acquired by the cell that has access to this information in particular conditions.

There is strong evidence to support the idea that this system, acquired by evolution and present in eukaryotes, has been transmitted to human cells.

The search for an "*SOS*" programme in eukaryotes and in multicellular organisms such as ours has already produced positive results. Professor Israel's studies have led to a search for homologies between the proteins and genes of the bacterial "*SOS*" system and those contained in our cells (Israel 1996).

One of these genes has already been identified. There is a very marked homology between the RecA bacterial

protein and a protein present in our cells, Rad 51. We thus have justified reasons for believing that the "*SOS*" system can also exist in our cells, even in a much more developed version. On closer examination, the current dominant model of malignant development being the result solely of chance, i.e. produced by a number of subsequent but always casual mutations, does not hold good due to the fairly predictable nature of the malignant development. Except for the initial events, certainly due to casual mutations, the progression of the tumoural disease is undoubtedly a stereotype, closely following a predefined script.

The tumour cells gradually acquire more and more properties and characteristics and "learn" to carry out a series of activities. Such a phenotype requires around one thousand generation cycles to develop. Considering that each generation cycle takes around 48 hours, in a relatively short period of time the tumour cells are able to produce growth factors that their non-endocrine homologues are unable to synthesize. The tumour cells express receptors to these factors, which influence selective proliferation limited to these neoplastic populations.

The tumour cells also become increasingly mobile and deformable in order to better reach the capillaries and increase their metastatic potential; they also acquire the ability to survive and proliferate in different types of parenchymal tissue, and to coat themselves with molecules that protect them from the immune system. They then become able to secrete proteases which, by dissolving the membranes, allow the invasion of adjacent cells as well as inducing angiogenesis and local and systemic immunodepression. A study published in 2003 in "Nature" reports how a melanoma cell attacked by a lymphocyte can produce "apoptosis" of the lymphocyte; the neoplastic populations thus gradually acquire the ability to eliminate the cells of the immune system that attempt to attack the tumour cell.

Lastly, the tumour cell is able to modify the surrounding cellular environment, inducing the adjacent cells to support its proliferation.

The very fact that the tumour cell can easily encode the essential steps of its progression towards malignancy, and gradually increase its aggressiveness, proliferation and adaptation, contradicts the concept of a strictly casual development of the tumoural disease.

There are additional aspects which support this theory; the paraneoplastic syndromes, a sort of litmus paper of the progression towards malignancy. One significant particular consists of the fact that if these mutations were governed by chance, or better if their progression were totally governed by chance, then we would see both favourable and unfavourable mutations, or in any case mutations that were neutral compared with development of the tumour. But this is not in fact the case. The paraneoplastic syndromes show that tumour cells only produce substances that are of biological use to the tumour (Israel 1996).

This is in strong opposition to the official oncology concept of casual progression, since in this case we would also see the production of substances that are neutral or at least unfavourable to the progression of the tumour. There are some genetic events that characterise the progression of the tumour which are not mutations but merely reactivations and repressions or amplifications of genes that are not mutant but silent.

This inevitably leads us to conclude that the more evolved multicellular organisms such as ours have certainly inherited parts of a genome from bacteria, as clearly reported by recent studies of molecular genetics which show that certain bacterial genes have been totally preserved in our cells.

In the evolution of multicellular organisms towards increasingly more complex forms, the destiny of every cell is linked to the destiny of the community to which it belongs.

Evolution towards complexity, towards a multicellular organism, foresees a sort of cellular community cooperation and thus the introduction of new rules. In this sense, evolution has set up a kind of counter-programme or system that controls tissue homeostasis, something which is obviously not possible or necessary in a bacterial or unicellular environment.

This is the system of the oncosuppressors, which ensures antiblastic cellular homeostasis and prevents each individual cell from freeing itself and becoming independent, a process which could put the entire tissue community at risk.

Evolution produced this oncosuppressor system which is certainly still young, and thus more imperfect with certain deficiencies.

As a result, research has not yet found the homologues of oncosuppressors in the eukaryotes, and we thus have reason to believe that oncosuppressors are genes which evolved at a later stage.

One particularly interesting oncosuppressor is the p53 gene, the guardian of the genome, directly involved in activation of a cellular programme that is fundamental for antiblastic homeostasis, apoptosis.

I have talked at length about Radman's survival programme in order to highlight, also in view of the subsequent findings, the rationality of the criteria, the molecular mechanisms and the objectives of the DBM. The research carried out by Radman, accepted and developed by Professors Israel and Truc, presented at the 1st National DBM Conference in May 2004 (Di Bella 2005), and reported here, provide greater awareness that the protein-like ability of the tumour cell to adapt, to mutate and recover, and its formidable vitality, all features unknown to physiological human biology, have been seriously underestimated. An exact and realistic evaluation of the practically unlimited neoplastic biological potential leads to a therapeutic logic which conforms exactly to the claims and rationale of the DBM: only an early synergic and concentric multitherapy attack, without interruption, can stand up to, limit and

prevail over a form of life which is different and dramatically superior to physiological life, and which has an extremely high capacity to adapt to and overcome every single adverse condition that medicine can invent to fight it. The neoplastic cell therefore easily overcomes any obstacle, however efficient it is, and only the simultaneous activation of a series of blockades against the neoplastic mutations can prevent the tumour cell's most deadly mechanism of defence: mutation. Only the synergic factorial effect of the cytostatic and antiproliferative differentiating multitherapy components of the DBM can counter the exponential proliferation of the neoplastic phenotype and its very high mutagenic ability, an extremely efficient defence system that is difficult to penetrate. It is necessary to act on critical elements of the neoplastic process such as differentiation by the ***simultaneous*** activation of multiple differentiating receptor targets like the VDR (Vit D_3 nuclear receptors), RXR (retinoic acid nuclear receptor), RAR–alpha, beta, gamma (retinoic acid membrane receptors), and Mel-1,2 RZR/ROR (Melatonin membrane and nuclear receptors).***At the same time*** it is necessary to eliminate the greatest possible variety and amount of energy from the neoplastic cell, represented by GH, GF, and PRL, and in hormone-dependent tumours by estrogens and androgens. This objective is achieved by ***inhibiting the incretion*** of hypophysial GH and the relative GF by means of SST and its analogues, and of PRL with Bromocriptine and/or Cabergoline. An extensive review of the relative literature (around 2000 papers) is included in the volume "The Di Bella Method" (Di Bella 2005). MLT has a particular, determining and multifunctional effect, negatively regulating angiogenesis by inhibiting an essential component, PDGF, and by regulating (with a homeostatic mechanism of serotoninergic modulation also made possible by its binding of hydrogen with adenosine) the rate of thrombocythemia, platelet aggregation (synergically to Alfa MSH), vasal tone and endothelial permeability (through modulation of EDRF and EDCF), essential factors for the release of PDGF.

Innovative therapeutic targets of the DBM also include the homeostasis of the environment in which the tumour cell lives, the physiological regulation of the cellular membrane potentials, the basal membranes, which have proven differentiating activity, the adhesion proteins, the layers restricting expansion of the tumour, the entire extracellular matrix, the trophism and efficiency of the parenchyma, tissues, and endothelia with relative re-establishment at physiological level of the vasal permeability, and of the blood-tissue exchanges and perfusion. The formulations, posology and doses of MLT and the vitamin components of the DBM also enhance immunity.

The aims of the DBM include physiological recovery of the circadian biological rhythms that are destroyed in tumours, by modulating the bioavailability of the pineal indoles in a context of temporal therapeutic continuity, in the sense of a continuous assault on a tumour cell already sensitized by the numerous differentiating agents and from which hormones and growth factors have also been eliminated, without (unlike chemotherapy cycles) allowing it pauses in which to recover, all supplemented by minimal apoptotic, non-cytotoxic and non-mutagenic doses of chemotherapy, made more tolerant by the MLT (Pacini 2009) and the vitamins contained in the DBM.

CASE SERIES

Basis of this retrospective observational study

Since the end of the 1970s, a growing number of tumour patients in Italy have chosen to be treated with the Di Bella Method (DBM), conceived and progressively refined and supplemented by Prof. Luigi Di Bella, a doctor and scientist with additional degrees in chemistry and pharmacology, and a university lecturer in general physiology, human physiology and biochemistry, preferring this method to chemotherapy. The tolerability of this method and the positive results in terms of survival and quality of life led to an increasingly widespread use of the DBM (practised by thousands of patients), creating serious disputes between public opinion and health institutions, which tried to evade the growing request for the DBM to be made available free-of-charge with a phase II trial, the planning, conduction and conclusion of which were the cause of harsh criticism and discomposure, not only in public opinion but also among politicians, doctors and the media, up to the point of investigations by magistrates. The irregularities of this trial were also the subject of more than fifty parliamentary questions, published in the Official Gazette of the Italian Parliament. Regardless of the numerous and serious irregularities that were documented and also reported in the international literature, the Italian Institute of Health, which is responsible for medical trials, claimed that: «It was necessary to carry out a study without a control group since, in the situation that existed at the start of 1998, this was not conceivable…

It was not conceivable to carry out this type of study which is generally performed throughout the world, and also in Italy (but not for the DBM!?).

This reasoning does not hold up: in fact, when the DBM trial was published in the British Medical Journal, the editor, Marcus Muller, strongly criticised the design of the study (a very unusual occurrence), claiming that: The authors (of the trial report) state also that they would not have been able to perform a randomised clinical study for ethical reasons, but these reasons are not clear. In actual fact, it could be claimed that it was precisely the poor planning of the study that was anti-ethical.

And as regards the lack of a control group, this is what the researcher, Rey M.D., had to say in a letter to the B.M.J.: «What was the Di Bella treatment compared to? Nothing! It would have been much more useful to

compare the Di Bella treatment and conventional treatment». As we can see, the study design was considered to be poor, since two fundamental characteristics which give a study scientific proof were missing, i.e. randomisation and a control group.

The definitive denial of the conclusions reached by this study is further confirmed by the increasing number of reports in the literature on the antitumoural efficacy of the active ingredients of the DBM (somatostatin, retinoids, vitamin D_3, Melatonin, etc.), declared to be ineffective by the trial.

The numerous and serious irregularities of this trial include:

- the issuing of drugs that were beyond their expiry date to 1048 patients (documented and reported by the NAS (the police branch in Italy responsible for checks in the health sector).
- the imperfect preparation of the drugs (Prof. Di Bella's indications were not followed) was also ascerta – the presence of acetone, a notoriously toxic and cancerogous substance, in one of the trial drugs;
- the administration of only 4 of the seven drugs included in the DBM;
- the failure to use a timed system for the injection of somatostatin in a significant number of patients. This hindered the efficacy of somatostatin which, with a half-life of 3 minutes, has an efficacy strictly conditioned by delivery times of at least 8–10 hours with a timer;
- Evaluation times and criteria for cytolytic treatments were chosen instead of those for biological treatment, also disregarding the criteria of the National Cancer Institute (NCI) relative to the design and objectives of clinical trials. The NCI states, in fact, that the most reliable study designs are the double blind type with a control group, immediately followed by those with a control group, and at the lowest level, with the least scientific significance, a mere collection of clinical cases, which was the design used for the DBM trial. As far as objectives are concerned, the main objective for the NCI is survival, immediately followed by quality of life and, at the bottom of the list, the size of the tumour. This last objective, the least reliable one, was chosen for the DBM trial.
- The criteria for patient enrolment were anti-ethical with respect to those declared and reported by Prof Di Bella to the Ministry of Health, during meetings of the oncology committee for planning of the trial. Prof Di Bella declared that his method gave results that were directly proportional to the timeliness of the treatment, and inversely to the number and intensity of the chemo/radiotherapy cycles that the patient had undergone. Practically all the patients enrolled in the trial were critically and/or terminally ill and had repeatedly undergone chemo/radiotherapy.

Those responsible for the trial were tried but not charged as it was thought that the numerous and serious irregularities, not denied by the magistrates, were not due to criminal intent but to the hurried design of the trial, under the pressure of public opinion. The fact remains, and was not denied by the magistrates, that these irregularities deprived the trial of all scientific significance and clinical indications. They were denounced not only by the 50 parliamentary questions (reported in the Official Gazette of the Italian Republic) but also by the Italian press and television. They are fully documented in the book by Vincenzo Brancatisano "Un po' di verità sulla cura Di Bella" (A bit of truth about the Di Bella treatment), Ed Trawel Factory, 1999.An analysis of the entire design, conduction and conclusion of the trial, supported by original documents, ministerial reports, findings and checks is published in the monograph "Il Metodo Di Bella", Mattioli Editore, 3rd Edition, 2005 by the undersigned. This documentation totally delegitimises the trial.

I believe that this somewhat lengthy introduction was necessary because the objection could be raised that the trial in Italy in 1998 declared the DBM to be ineffective, and to explain the reasons that led to the first spontaneous, retrospective observational clinical study in Italy, set up solely as a result of public initiative to contest the results of the trial and vindicate freedom of choice for treatment. Thousands of patients in Italy have presented appeals to the magistrates for the right to receive the Di Bella treatment free-of-charge, and many still continue to present such appeals. Following the trial, more than two thousand rulings ordered the Italian Health Service to provide the DBM, on the basis of sworn experts' reports which certified the positive effects of the treatment in patients in whom chemotherapy and/or monoclonal antibodies had proved ineffective. We believe this should be pointed out, not only for its social importance, and the total lack of precedents, but also for the considerable amount of scientific and clinical data that has emerged.

We now report the data relative to 124 oncological patients examined by three doctors, appointed as "Technical Experts" by the Public Prosecutor's Office of Lecce, while another 104 cases are already present in the literature and reported in journals reviewed by Med-Line. Other cases, approximately 325, divided into homogeneous groups according to disease, will be published on www.metododibella.org when the statistics are complete.

After the trial, in addition to the administrative appeals aimed at obtaining the drugs free-of-charge, many patients also spontaneously sent their clinical notes to the Public Prosecutor's Office of Lecce which, being the first to order the Health Service to provide the DBM, had become a reference point. The technical experts divided the cases as follows:

A. patients who presented appeals to the Public Prosecutor's Office of Lecce to obtain the treatment;
B. patients who, angry about the evident and serious irregularities of the trial, had spontaneously sent their clinical notes to the Public Prosecutor's Office of Lecce to document the positive effects obtained with the DBM.

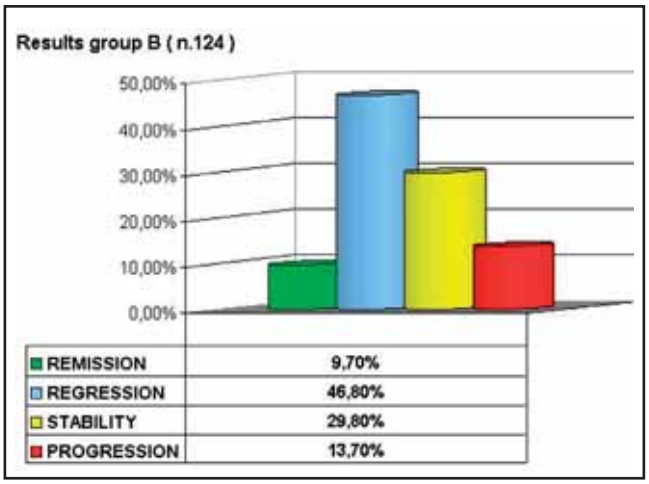
The difference between the two groups was above all the fact that group A, the great majority, consisted of patients wanting to try the DBM after the failure of chemotherapy, while in the second group, apart from a few exceptions, the patients had chosen the DBM as their first line therapy. This explains the appropriateness, for a realistic and reliable assessment of the DBM, of evaluating only group B, not "contaminated" by previous chemotherapy.

The report of the ruling issued by the Court of Lecce indicates an observation period which lasted for several years. Of the initial 126 cases, two died during treatment and 124 were monitored for more than 3 years, with a significant percentage of patients observed for more than 5 years. An analysis of the clinical records and the reports by the doctors who treated the 124 patients in group B provided the following data:

OVERALL RESULTS

localization	TOT	remission	regression	stability	progression
brain	10	2	3	3	2
neck	2	0	2	0	0
esophagus	3	0	1	1	1
liver	3	1	1	0	1
intestine	8	0	3	4	1
leukemia/lymphoma	24	3	14	5	2
breast	33	3	17	11	2
melanoma	1	1	0	0	0
ovary / uterus	2	0	1	0	1
pancreas	7	1	2	3	1
lung	16	1	5	7	3
prostate	3	0	2	1	0
kidneys	3	0	2	0	1
sarcoma	1	0	1	0	0
stomach	2	0	1	1	0
thyroid	4	0	1	1	2
bladder	2	0	2	0	0
total	124	12	58	37	17

TOT	remission	regression	stability	progression
124	12	58	37	17

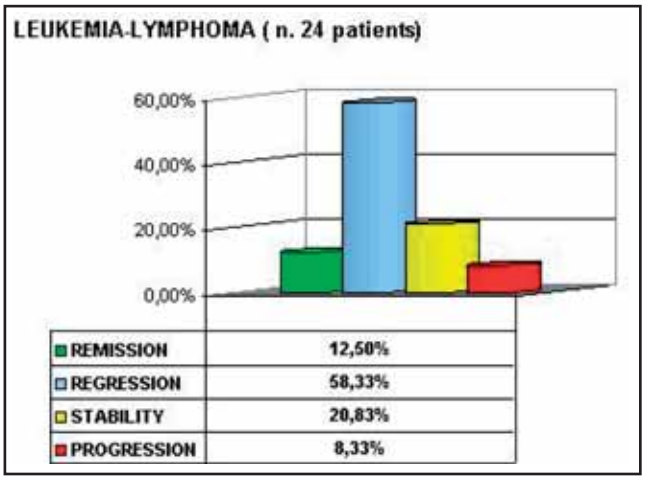


In particular:

Leukemia - Lymphoma

TOT	remission	regression	stability	progression
24	3	14	5	2

N.B: (1 of the 2 cases in progression did not use the correct amount of melatonin)



Breast

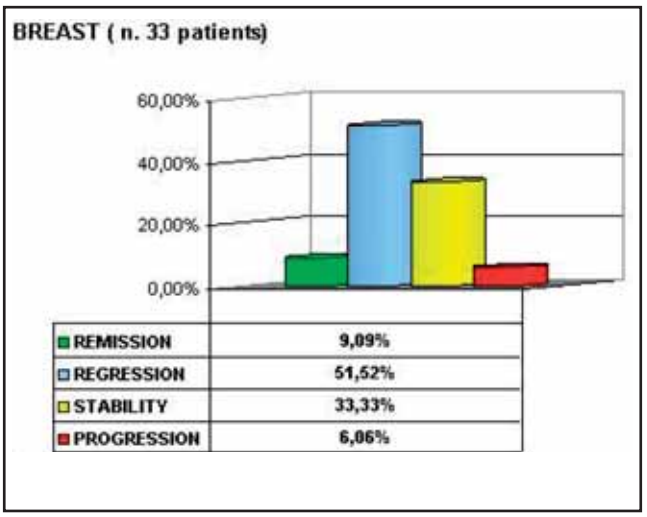
TOT	remission	regression	stability	progression
33	3	17	11	2

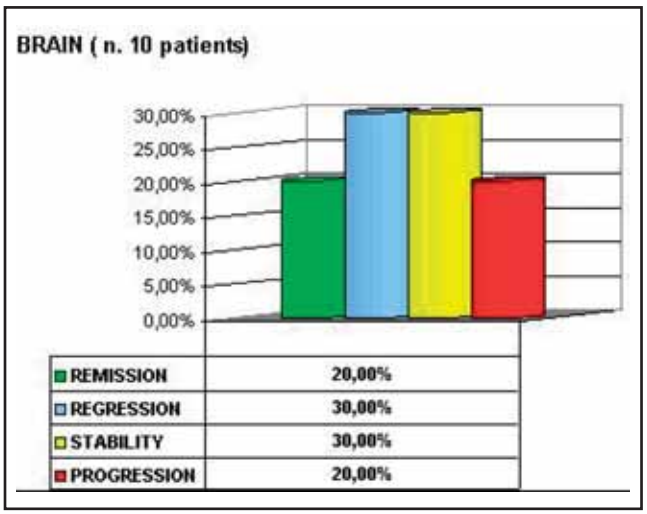
N.B: (the 2 cases in progression had previously undergone chemotherapy and had multiple metastases)

Brain

TOT	remission	regression	stability	progression
10	2	3	3	2

N.B: (the 2 cases in progression were: 1 who had previously undergone surgery, chemo- and radiotherapy, the other with incomplete documentation)



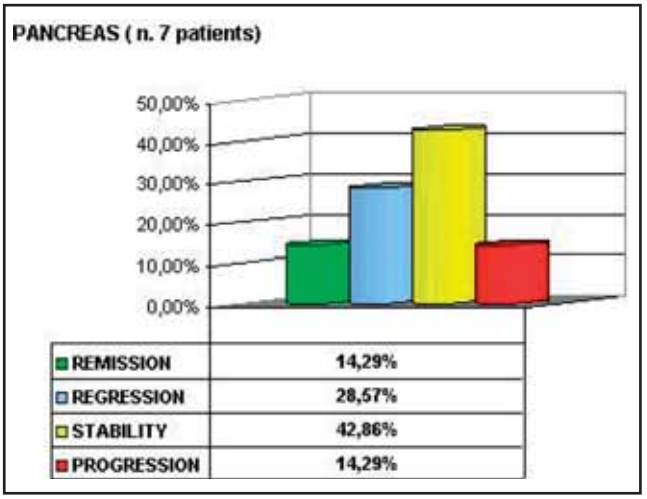


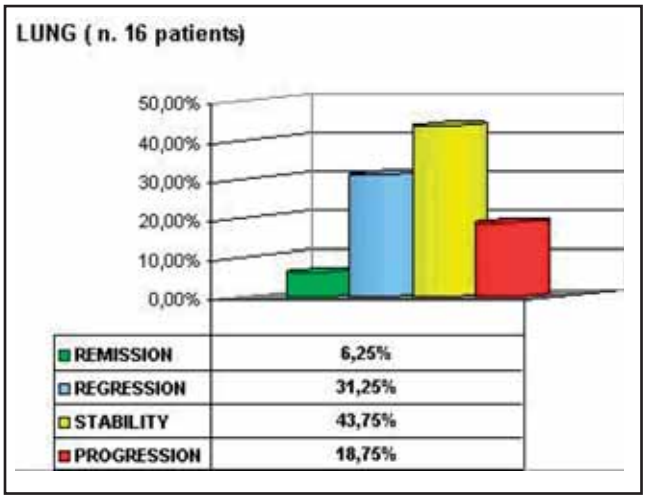
Pancreas

TOT	remission	regression	stability	progression
7	1	2	3	1

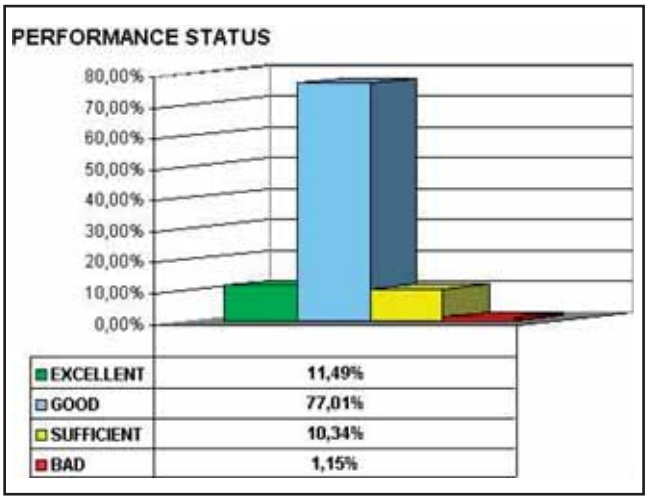
Lung

TOT	remission	regression	stability	progression
16	1	5	7	3





It was also possible to measure the data on the quality of life of these 124 patients:



The conclusions and reports of the 3 experts of the Court of Lecce on the total number of fully documented cases led to a clear declaration of efficacy and tolerability of the DBM.

On the basis of these sworn reports, the Magistrate declared that:

The considerable amount of clinical documentation acquired during these proceedings unquestionably show that many patients, not included in the trial, have obtained positive results with the DBM, not only as regards an improvement in quality of life, but also in terms of blocking or regression of the disease.

The reports by doctors, patients and relatives of patients on the total or partial recovery of health following application of the Di Bella treatment (..and) the technical experts' reports (…show that) all (the patients) had an improvement in their quality of life (…) and are having positive results thanks to the considerable extension in survival with respect to the initial unfavourable short-term prognosis (just a few weeks of life).

In conclusion, the DBM seems to have determined an improvement in the quality of life in most of the treated cases. ***No side effects of the DBM have ever been noted.***

We are not unaware of the contrast between the results of the technical experts and the conclusions of the official trial (…).The improvement in the conditions of life of the tumour patients as a result of taking the drugs prescribed by the DBM is a fact that is more than sufficient to justify the administration of this treatment, and this is related to protection of the absolute legal right to health, referred to in art. 32 of the Constitution, which would otherwise be seriously and irreparably compromised.

These conclusions of a magistrate, based on clinical reports, witness statements and data validated by sworn experts' reports, are scientifically significant and merit careful and detailed examination. They are in radical contrast to and belie the conclusions of the DBM trial, the irregularities of which and the completely unreliable design, conduction and conclusions are by now well known and fully documented.

Adding the following data to these 124 cases certified by the experts of the Court of Lecce provides an overall picture of the statistics:

54 cases published in the journal of the association of doctors who, in Italy, apply the DBM:
23 cases of non-Hodgkin's lymphoma
26 cases of breast cancer
2 cases of small cell lung cancer
1 case of osteogenic sarcoma
1 case of pleural mesothelioma
1 case of brain tumour
making a total of 54 cases

Reports on the results of the DBM presented at the 1st and 2nd National DBM Conferences, at the Conference on Biological treatment of neoplastic and degenerative diseases and at the 95th National Conference of the SIO (Italian Society of Otorhinolaringology), Turin 2008:

122 cases presented at the 1st national DBM Conference in Bologna 2004

1 case of multiple myeloma
1 case of astrocytoma
1 case of mucinous adenocarcinoma of the ovary
1 case of metastatic adenocarcinoma of the sigmoid colon
1 case of pleural mesothelioma
1 case of non-Hodgkin's lymphoma
1 case of cholangiocellular adenocarcinoma
4 cases of non-Hodgkin's lymphoma
2 cases of metastatic breast cancer
1 case of hepatocarcinoma
1 case of ovarian cancer
2 cases of adenocarcinoma of the pancreas
11 cases of pleural mesothelioma
76 cases of lung cancer
1 case of multiple adenomatosis of the liver
2 cases of lung cancer
1 case of sarcoma
1 case of leiomyosarcoma
2 cases of rectal colon cancer
1 case of non-Hodgkin's lymphoma
1 case of cancer of the larynx
1 case of pleomorphic liposarcoma
1 case of pleural mesothelioma
1 case of gastric lymphoma
1 case of non-small-cell pulmonary adenocarcinoma
1 case of epidermoid lung cancer
3 cases of gastric cancer
1 case of sarcoma
1 case of hepato-pancreatic cancer
1 case of pleuropulmonary undifferentiated cancer
1 case of breast cancer

Total: 222 cases

120 cases presented at the 2nd national DBM Conference in Milan 2005

28 cases of non-small-cell lung cancer
46 cases of small-cell lung cancer
2 cases of non-Hodgkin's lymphoma
1 case of chronic lymphatic leukemia
17 cases of pancreatic cancer
6 cases of breast cancer
1 case of anaplastic lung cancer
1 case of non-Hodgkin's lymphoma
2 cases of non-Hodgkin's lymphoma
4 cases of exocrine pancreatic cancer
1 case of sarcoma
2 cases of metastatic breast cancer
1 case of multiple myeloma
1 case of non-Hodgkin's lymphoma
1 case of breast cancer with pulmonary disssemination
4 cases of non-Hodgkin's lymphoma
2 cases of metastatic breast cancer
1 case of hepatocarcinoma
2 cases of sarcoma

Total: 120 cases

12 cases presented at the Conference on January 16 2010 at the Republic of S Marino on "Biological treatment of neoplastic and degenerative diseases"

4 cases of lymphoblastic leukemia
1 case of neuroblastoma
1 case of renal carcinoma
2 cases of breast cancer
1 case of cancer of the thyroid
1 case of hepatocarcinoma
1 case of leiomyosarcoma
1 case of testicular cancer

Total: 12 cases

The proceedings of these three conferences above have been published and are available on the Di Bella Foundation portal www.metododibella.org

18 cases presented at and published in the proceedings of the 95th National Conference of the SIO (Italian Society of Otorhinolaringology) Turin 2008.

103 cases in journals reviewed by Med-Line
20 cases of non-Hodgkin's lymphoma published in Cancer Biotherapy
4 cases of lymphoblastic leukemia published in Cancer Biotherapy
1 case of non-Hodgkin's lymphoma published in Am. J. Therapy
1 case of non-Hodgkin's lymphoma published in Am. J. Therapy
1 case of breast cancer published in Neuro Endocrinol Lett
1 case of cancer of the esophagus published in Neuro Endocrinol Lett
1 case of neuroblastoma published in Neuro Endocrinol Lett
74 cases of lung cancer published in Cancer Biotherapy,

Total of 103 cases

Overall number of patients treated with the DBM: 553 cases

DISCUSSION

A series of data can be pointed out that, albeit with different frequencies, times, methods and intensity in the various types of tumour, are common or relatively frequent findings.

- A general increase in life expectation, and an improvement in the quality of life with respect to current oncological therapies, a decrease in the frequency, number and extent of metastases, and a greater limitation and control of the progression of both primary and secondary lesions. The time necessary for an objective response to the DBM in most cases is at least 4 months, while in cases in which remission is achieved with a complete objective response this takes at least 14 months. In this situation, the dosage of the individual components should be reduced very slowly and gradually, particularly the dose of somatostatin, over a period of around one year. Small doses of the mixture of retinoids and MLT continue for the prevention of recurrences and the antidegenerative and immunostimulating effect.
- Reduction of the metabolic activity of the tumour cell population, shown by PET, associated with limitation and/or elimination of the neurological, vascular, inflammatory paraneoplastic syndromes, etc.
- Greater control of secondary osteolytic lesions, better ability to restore metabolism, trophism and functionality of the osteocartilaginous tissue, the epithelia and the extracellular matrix to physiological levels.
- Improvement of cenesthesia, appetite, neuromuscular functionality, trophism of the parenchyma, tissues and endothelia with physiological regulation of their permeability and consequently of blood-tissue exchanges.
- Cleansing and re-epithelization of mixed inflammatory-neoplastic focuses.
- Improvement of the visceral micro and macrocirculation.
- Psychophysical improvement, also observed in seriously affected and critically ill subjects.
- Reduction for varying lengths of time of the speed of progression with stabilization of tumour diseases which have already started to progress rapidly before beginning the DBM.
- Possible control and/or reduction of pain with decreases in the doses or discontinuation of painkillers.
- Shift towards physiological parameters of platelet aggregation and tolerability of the minimal and continuing doses of cyclophosphamide or oncocarbide due to the myeloprotective effect of complexed MLT and the DBM compound of retinoids.
- Improvement in immunity with reduction in the onset of inflammatory processes, more easily controllable.
- Inversely proportional rapidity of subjective and objective response of the DBM to:
  - the intensity and number of chemotherapy cycles carried out;
  - the time interval from onset of the tumour;
  - the radiotherapy cycles carried out (except for stereotaxic radiotherapy)
  - the clinical condition of the patient at the start of the DBM.
- If the DBM is administered simultaneously with radiotherapy, it has both a radioprotective and radiosensitizing effect.
- On stabilization of tumours in progression before treatment with the DBM, there is frequently a co-existence of the tumour with an acceptable quality of life that can allow a partial or total return to work. This sort of patient-tumour homeostasis may be observed for a year or more, even in patients who seemed to be terminal, if the patient‘s condition is not severely and immediately impaired by the functional insufficiency of vital organs, and more frequently if repeated and exacting chemotherapy cycles have not been undergone.
- If the DBM is administered together with the chemotherapy protocols, it considerably reinforces the antiblastic effect, notably reducing the toxicity and the mutagenic effect.
- When tumour progression is present, this is much slower and more gradual than in similar situations in which the patient is treated only with chemo and/or radiotherapy.
- In the rare cases in which it is possible to start the DBM at least 20–30 days before surgical removal of the tumour, recurrences have rarely been observed. In operable tumours, the best results are obtained by preceding, accompanying and following surgery with the DBM, with a net reduction of the possible intraoperative seeding of tumour cells due to the opening of blood and lymph vessels and of the tissues restricting the expansion of the tumour, as well as the strong and documented activation by surgery of neoplastic angiogenesis. A net impairment of immunity, above all of interleukin 2, due to surgery has also been reported.
- After a period of more or less prolonged stability, progression may often occur, but in a number of cases varying according to tumour type and stage there is a slow and gradual reduction in volume and number of the primary and secondary lesions and, according to the histological features, complete remission
- Greater evidence of the rapidity and frequency of positive responses in terms of remission, and improvement in quality of life and objective responses are found in decreasing order in Hodgkin‘s and non-Hodgkin‘s lymphoma, LLC, neuroen-

docrine tumours, tumours of the thyroid, especially medullary and papillary, neuroblastomas, chemodectomas, glomic tumours, breast cancer, sarcomas, cancer of the upper aerodigestive epithelia, exocrine glandular appendage-cell tumours, prostate cancer and bladder cancer.

- A reduced response in terms of frequency of stabilization, remission, increase in quality of life (but for survival median values, quality of life and tolerability of the treatment are undoubtedly superior to chemotherapy) in non-small-cell lung cancer, while small-cell lung cancer, exocrine tumours of the pancreas, hepatocarcinoma, colorectal cancer, stomach cancer, renal cancer, cancer of the uterus, ovarian cancer and mesotheliomas respond better.
- In melanomas, glioblastomas, cholangiocarcinomas, and metastatic clear cell renal cancer, the median survival rates are lower than the above-mentioned ones; the same applies to remissions and control of locoregional extensions and/or remote dissemination, even though in these forms, as in the previous ones, the median survival rate relative to each stage, the quality of life and the tolerability of the treatment are greatly superior to the common forms of chemotherapy.
- In all cases, with rare exceptions, there is an evident improvement in quality of life, common to all types of tumour treated with the DBM; there is also a significant absence of toxicity, with the exception of a certain degree of drowsiness due to the MLT and of transitory toxicity relative to nausea and diarrhea. These symptoms are never severe and are only temporary thanks to the physiological compensation mechanisms and to the possibility of adjusting the timing of administration of MLT, mainly during the night hours, and of somatostatin at least 3 hours after supper, adjusting the timed infusion to 12 hours.
- With the DBM it is much more unlikely for neoplastic cachexia to occur in terminal patients, but before death these patients are often saved dramatic decline and severe suffering.

CONCLUSIONS

The number of clinical cases monitored, the period of observation, which in many cases was more than five years, and the great variety of neoplastic histotypes make it possible to draw preliminary conclusions limited to the median survival rates, the quality of life and the tolerability of the DBM. We consider these data as preliminary, even though they are documented, since they are the results of a retrospective observational study and because the division into homogeneous diseases and the statistical processing of the objective responses of the individual diseases are still in progress, although close to publication. We do point out, however, that the National Cancer Institute puts survival of the tumour patient in first place and quality of life in second place in the objectives of a clinical study. These data are not, therefore, without dignity and scientific importance.

A review of the overall statistics shows and evident uniformity of data relative to median survival and quality of life. The results published in the proceedings of the 4 conferences, in Italian journals (not reviewed by Med Line), international journals reviewed in Med Line, and of the case series certified by the Court of Lecce are substantially identical.

In all the tumours treated with the DBM, albeit with important differences between t hem, a net increase can be seen in life expectation and an improvement in quality of life, without any significant toxicity compared with the data in the literature relative to the same types of tumour and at the same stages.

It is clearly demonstrated that the response to the DBM is directly proportional to the timeliness of the treatment and inversely proportional to the number and intensity of chemo-radiotherapy sessions carried out.

If the DBM precedes such treatment, recurrences are a much rarer event compared with the data in the literature.

We believe that a comparison of the documented scientific bases, the linear and mathematical logic of the rationale of the DBM, and the significant results with the severe and known limits of the current antitumoural treatments can lead to a greater interest in the prospects opened up by the DBM. A tumour is a deviation from normal life, which can be corrected by the DBM, supporting and enhancing vital reactions. The Di Bella Method is not, therefore, an „alternative", in the common meaning of the term, but a rational integration and the convergence of definitively acquired medical-scientific knowledge and emerging scientific evidence in clinical medicine liberated from political-financial contamination.

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