BIT Life Sciences' 3°

World Cancer Congress-2010

Singapore

The Di Bella Method

Title

Biological Oncotherapy According to The Di Bella Method (DBM), With The Synergic Use of Somatostatin and/or Octreotide, Bromocryptin and/or Cabergoline, Melatonin, Retinoids, Vitamins E, D3, and C, Chondroitin Sulfate, Calcium, and Minimal Apoptotic, Non Cytolytic Doses of Cyclophosphamide or Oncocarbide. Rationale of The DBM, and Results of 553 Cases of 29 Different Histotypes

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

Fixed part

- **Somatostatin and/or Octreotide**
- **Retinoid solution in Alpha tocopheryl acetate**
- **Melatonin chemically complexed**
- **Dihydrotachysterol,** (Synthetic D3)
- **Vitamin C**
- **Calcium**
- **Chondroit Sulfate**
- **Cyclophosphamide or Hydroxyurea (minimum doses)**
- **Bromocriptin and/or Cabergoline**

Retinoid solution in 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 1000 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.

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.

- **Somatostatin** ,peptide with 14 amino acids 3mg per day injected slowly subcutaneo usly or intravenous with a 12-hour And/Or

- **Octreotide** peptide with 8 amino acids 1 mg

per day injected slowly subcutaneo usly or intravenous with a 12-hour

- or Octreotide LAR 10 mg intramuscolar injection every 7 days)

B) Variable part

- Estrogen inihibitors
- Androgen inihibitors
- Glyphosine
- Anhydromethylencitrate of-hexamethylen tetramine
- Dibromomannitol
- Syntetic ACTH
- Isoniazid
- Erytropoietin

- Lenogastrim or Filgastrim
- Human albumina 20-25%
- Lisozyme
- Immunoglobulin
- Phenyl-quinoline-carbonic acid
- -Taurine
- -Levofolin
- Selenium methionine

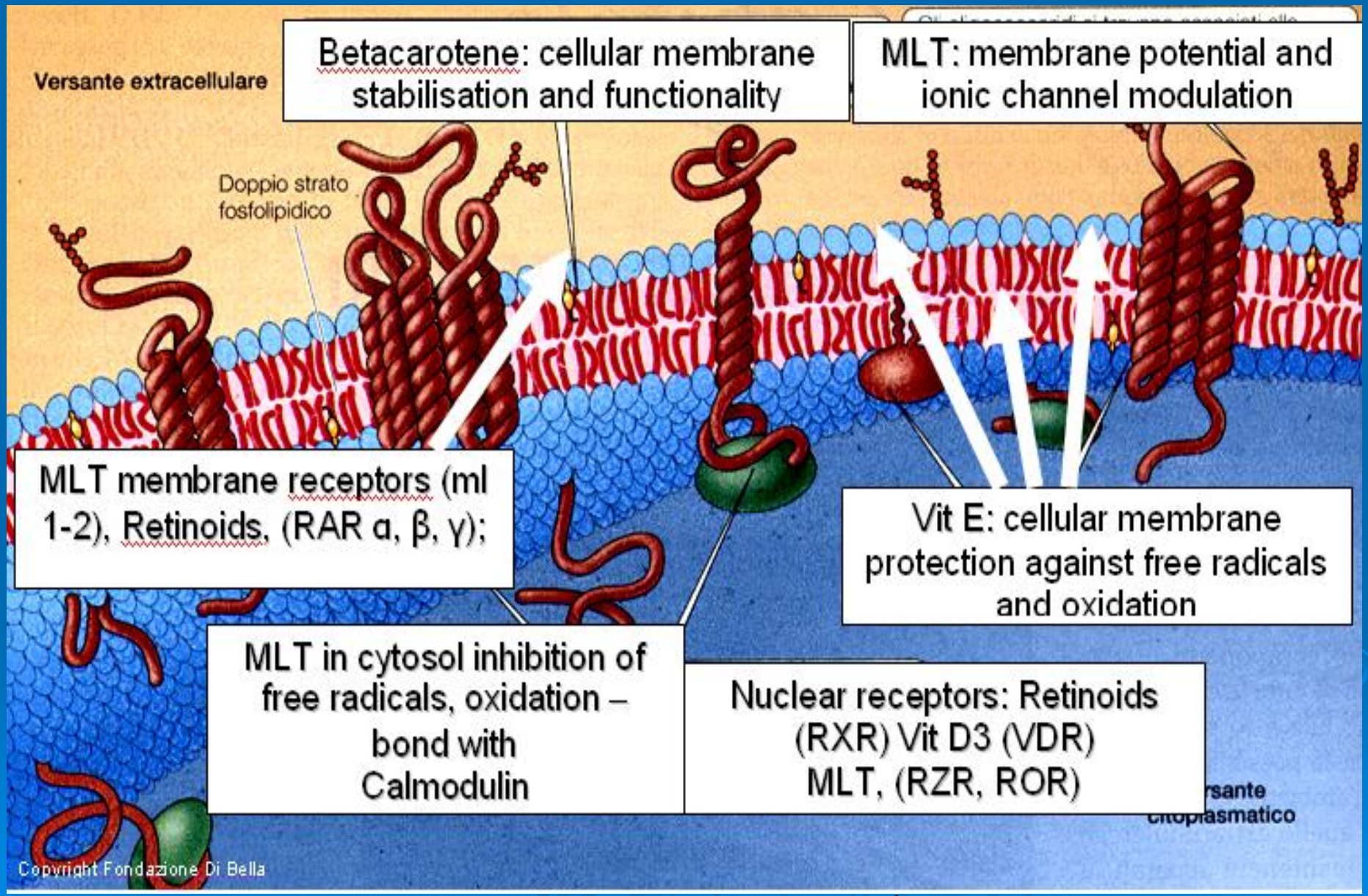
The DBM has 3 main objectives:

a) Defence against neoplastic aggression

b) Inhibition of neoplastic proliferation

c) Contrasting the marked mutagenic tendency of the neoplastic phenotype.

a) Defence against neoplastic aggression



a) Defence against neoplastic aggression

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.

b) Inhibition of neoplastic proliferation

GH
Growth Hormon
Central function of the in tumor onset and progression

Lincoln DT et al. – Histochem Cell Biol 1998 Feb;109(2):141-59

PRL
Prolactin
important function in tumor onset and progression,

Ben-JonathanNet al Trends Endocrinol Metab.2002;13(6):245-250

Growth Hormon [GH] Central function of the GH , in tumor onset and progression

Lincoln DT et al. – Histochem Cell Biol 1998 Feb;109(2):141-59

GH-dependent satellite growth factors decisive for oncogenesis

GH

EGF FGF IGF1 HGF NGF PDGF VEGF TGF CHOLECYSTOKININ VIP GASTRIN

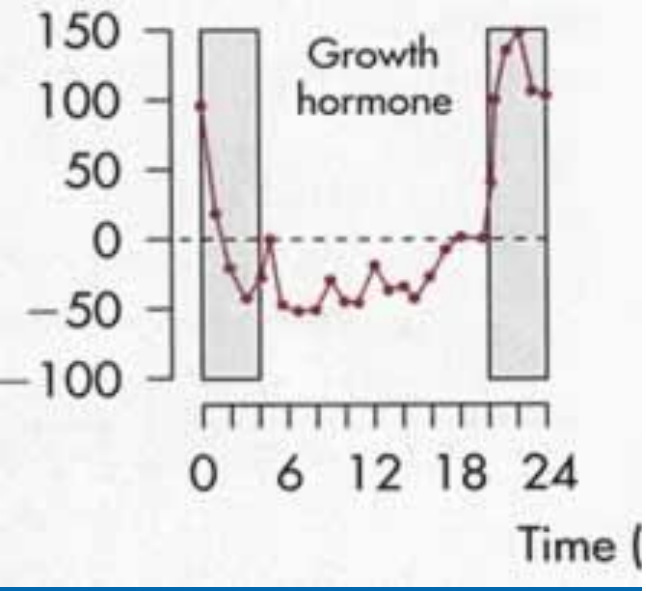
Growth factors decisive' for angiogenesis

FGF IGF1 HGF PDGF VEGF TGF VIP

Molecules which contribute to the promotion of angiogenesis

Interleuckin 8, Monocyte chemotaxis, eNos (endothelial nitric oxide synthase) Prostaglandin E2

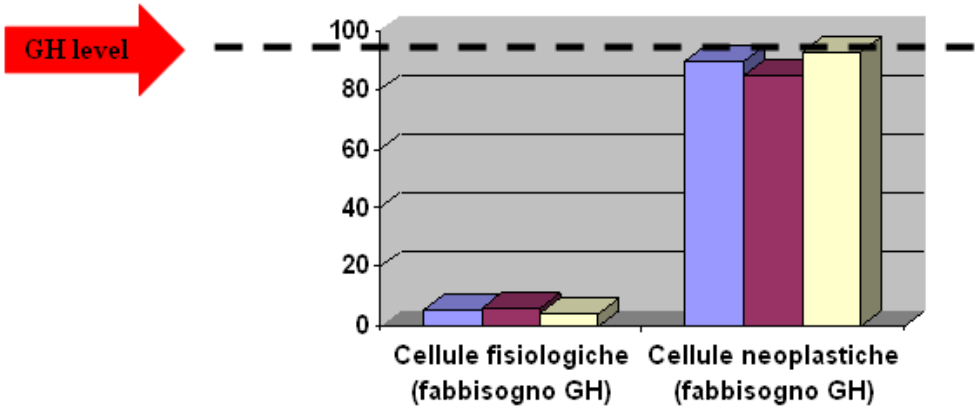
The GH-dependent growth factors that carry out a leading role in neoplastic induction and progression include epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), IGF 1-2 produced by the liver, nerve growth factor (NGF), platelet-derived growth factor (PDGF),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



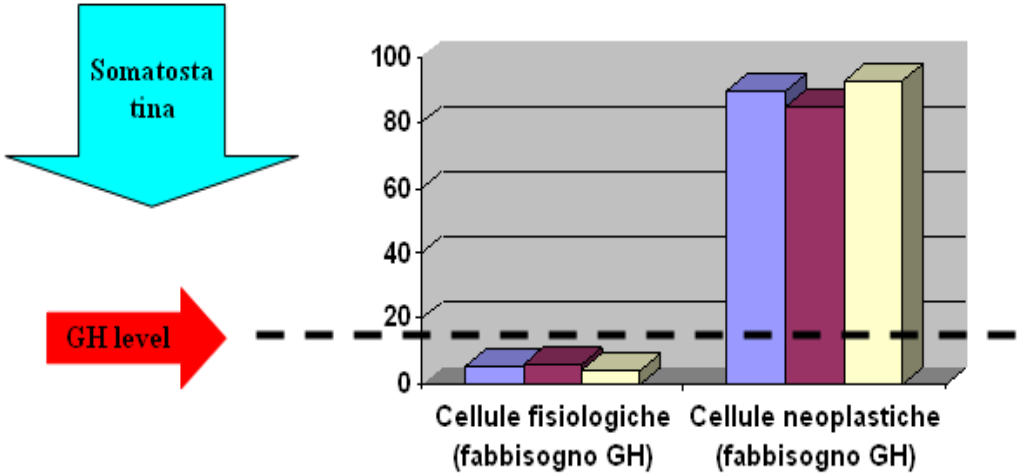
The doses and methods of administration of Somatostatin foreseen by the DBM make it possible to lower the plasma concentrations of circulating GH, while maintaining a sufficient level to ensure the indispensable use by the various physiological districts.

The

Livello fisiologico del GH

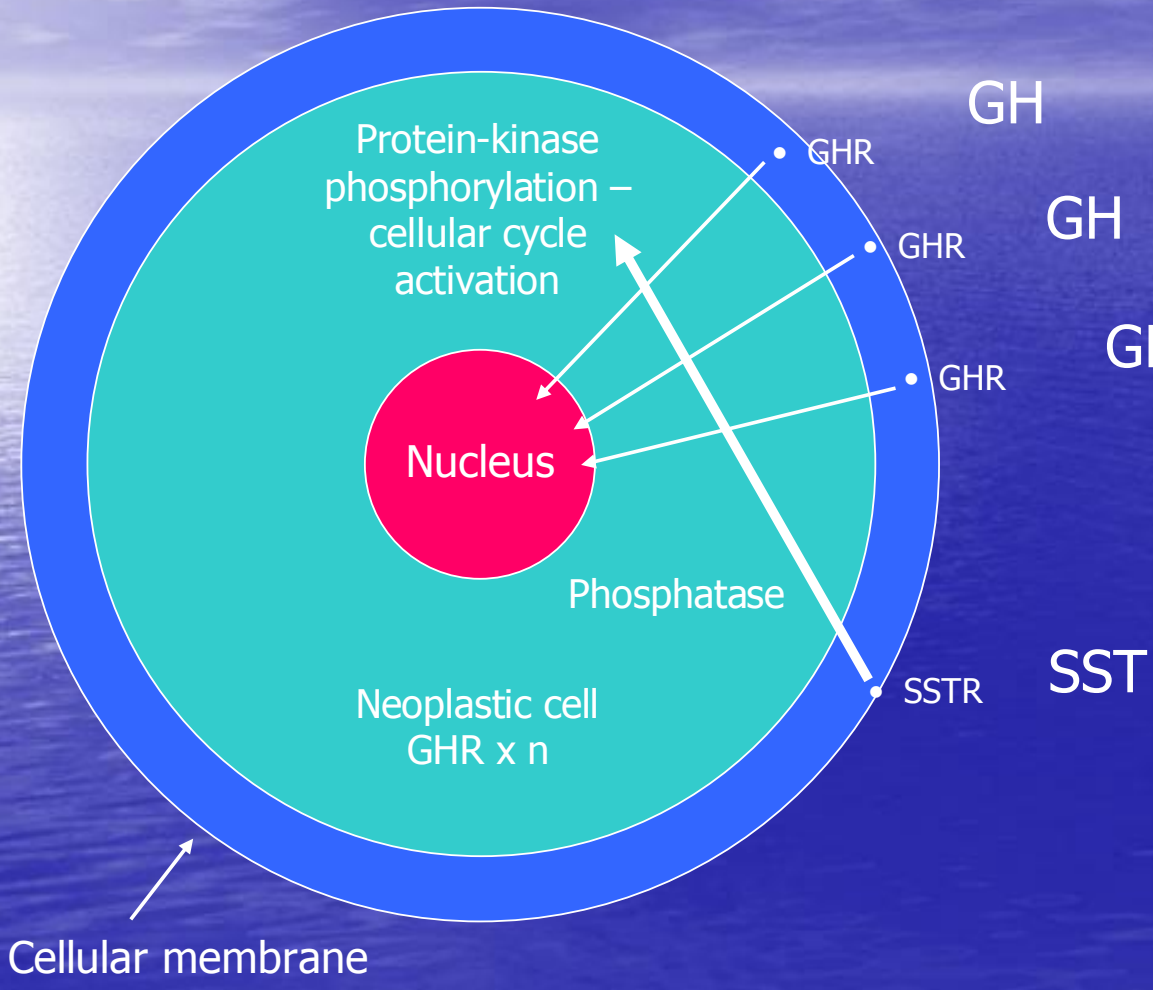


Livello del GH dopo somministrazione di Somatostatina

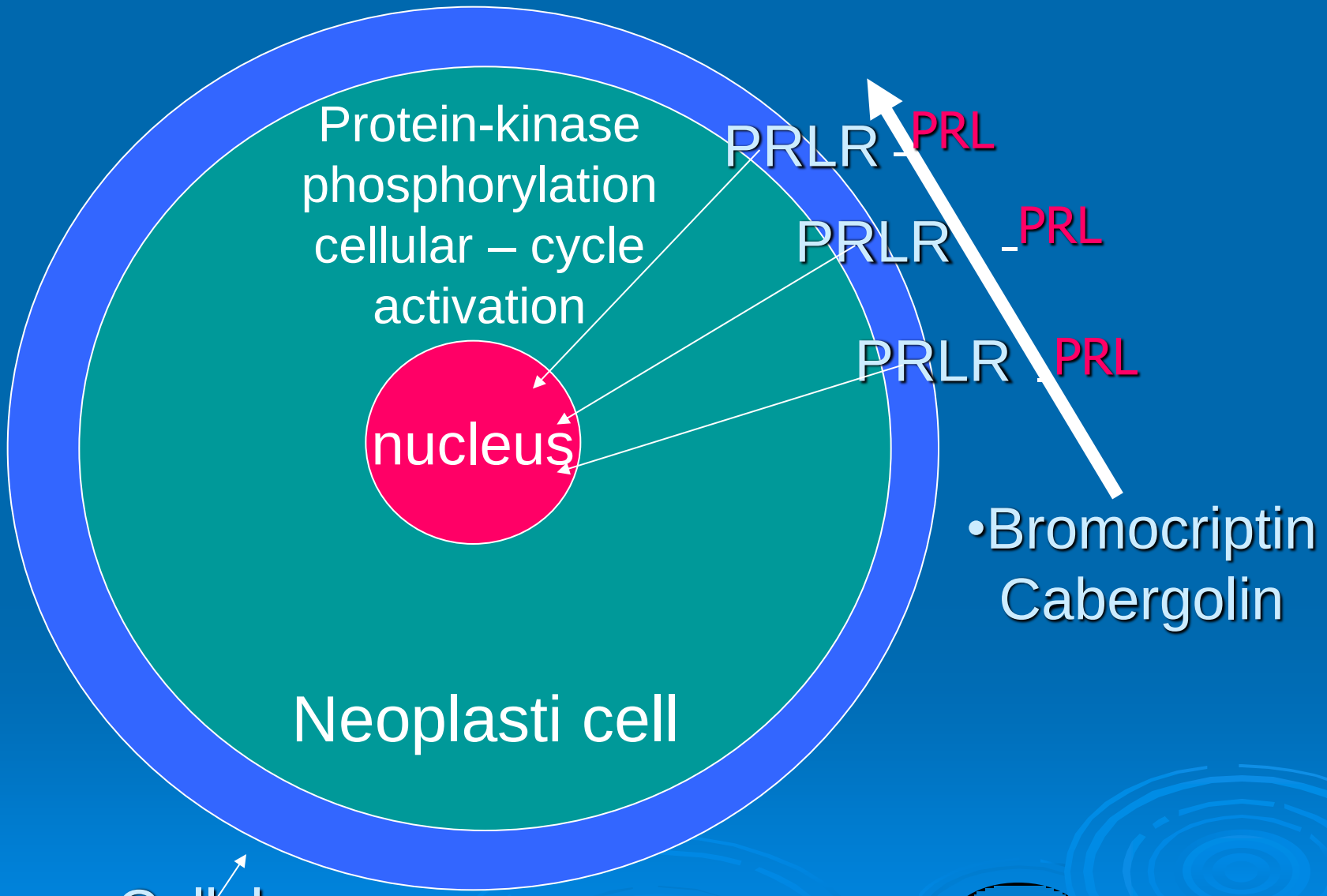


The doses and methods of administration of Somatostatin foreseen by the DBM make it possible to lower the plasma concentrations of circulating GH while maintaining a sufficient level to ensure the indispensable use by the various physiological district

Neoplastic proliferation

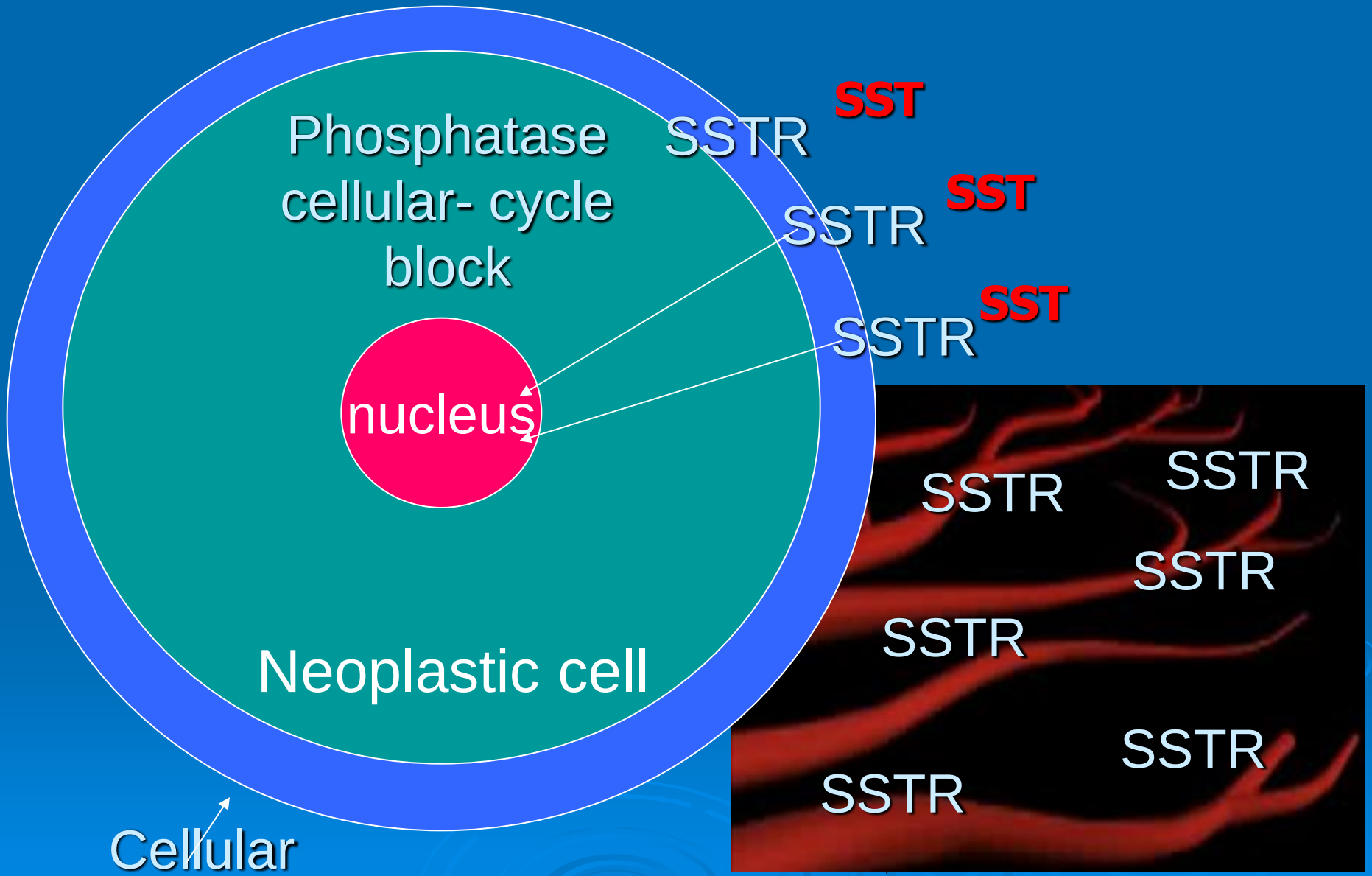


Control of neoplastic proliferation



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.*

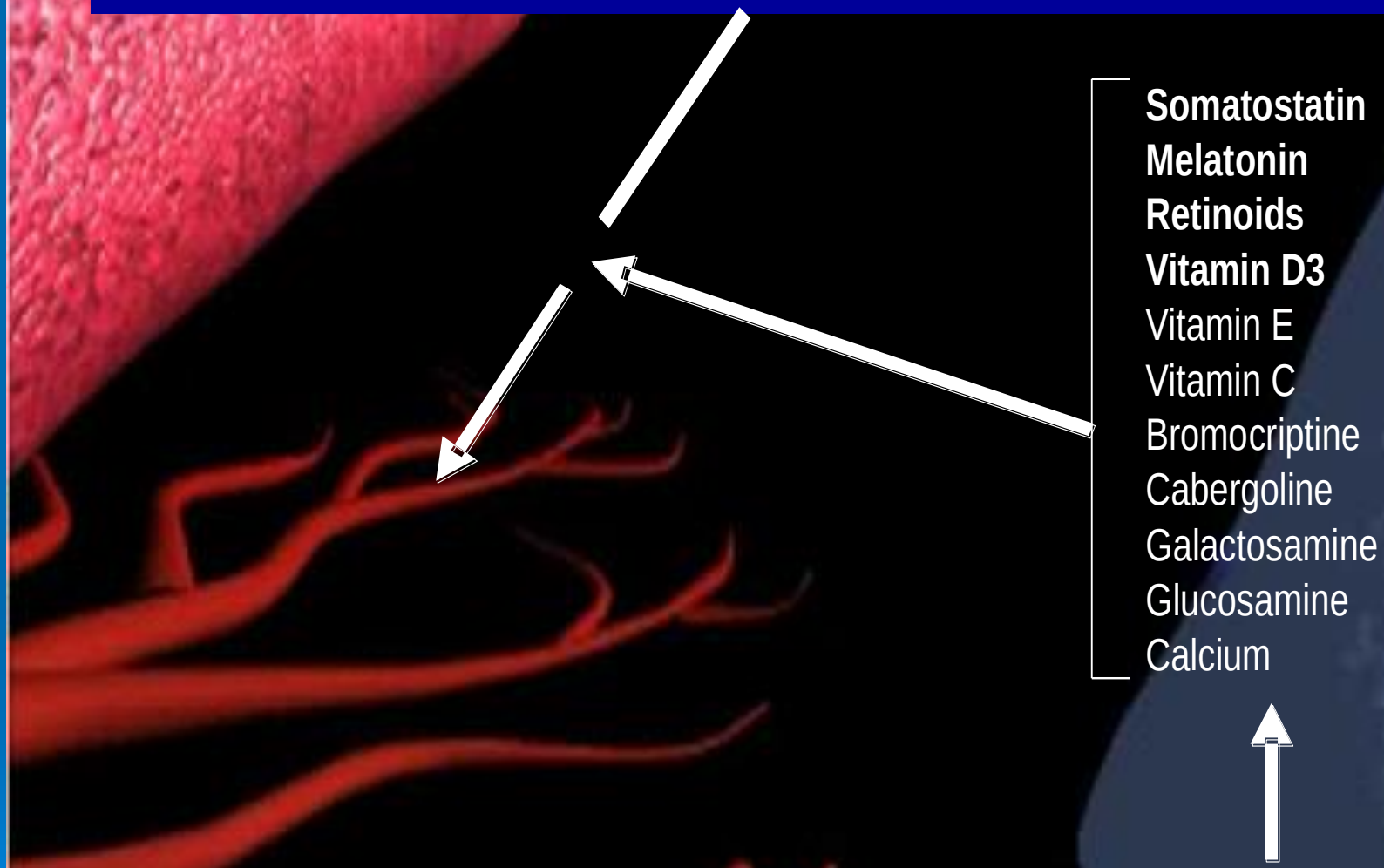
Control of neoplastic proliferation



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.*

Angiogenesis factors

FGF IGF1 HGF e-Nos (CM) PGE2 Interl. 8 PDGF VEGF TGF VIP



Somatostatin
Melatonin
Retinoids
Vitamin D3
Vitamin E
Vitamin C
Bromocriptine
Cabergoline
Galactosamine
Glucosamine
Calcium

DBM molecules inhibiting Angiogenesis

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)*

c) Controll of cellular differentiation

Phosphorylation
acetylation
methylation

- RAR α β γ
- ML 1-2 R
- ECMR

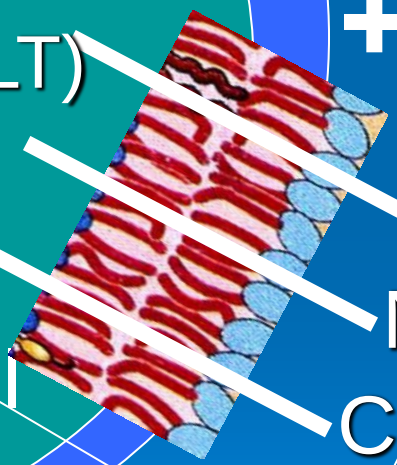
membrane receptors

nuclear receptors

VDR (Vit D3)
RZR α β
ROR
RXR
(Ac retinoic)

(MLT)

MELATONIN and Cytochalasin B regulates the cellular membrane potentials and thus also the ionic channels and the permeability of the membrane



Neoplastic cell

Cellular membrane

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.***

Case series
retrospective observational study of patients treated with the DBM
Overall number : 553 cases

1)
124 cases Adding the following data to these certified by the experts of the Court of Lecce
provides an overall picture of the statistics:
2)
103 cases in journals reviewed by Med-Line
3)
54 cases published in the italian medical journal Skepsis of the association of doctors who, in Italy, apply the DBM
4)
122 cases presented at the 1st national DBM Conference in Bologna 2004
5)
120 cases presented at the 2nd national DBM Conference in Milan 2005
6)
12 cases presented at the Conference on January 16 2010 at the Republic of S Marino on
"Biological treatment of neoplastic and degenerative diseases"
7)
18 cases 95th National Conference of the Italian Society of Otorhinolaringology, Turin 2008

1)
124 cases Adding the following data to

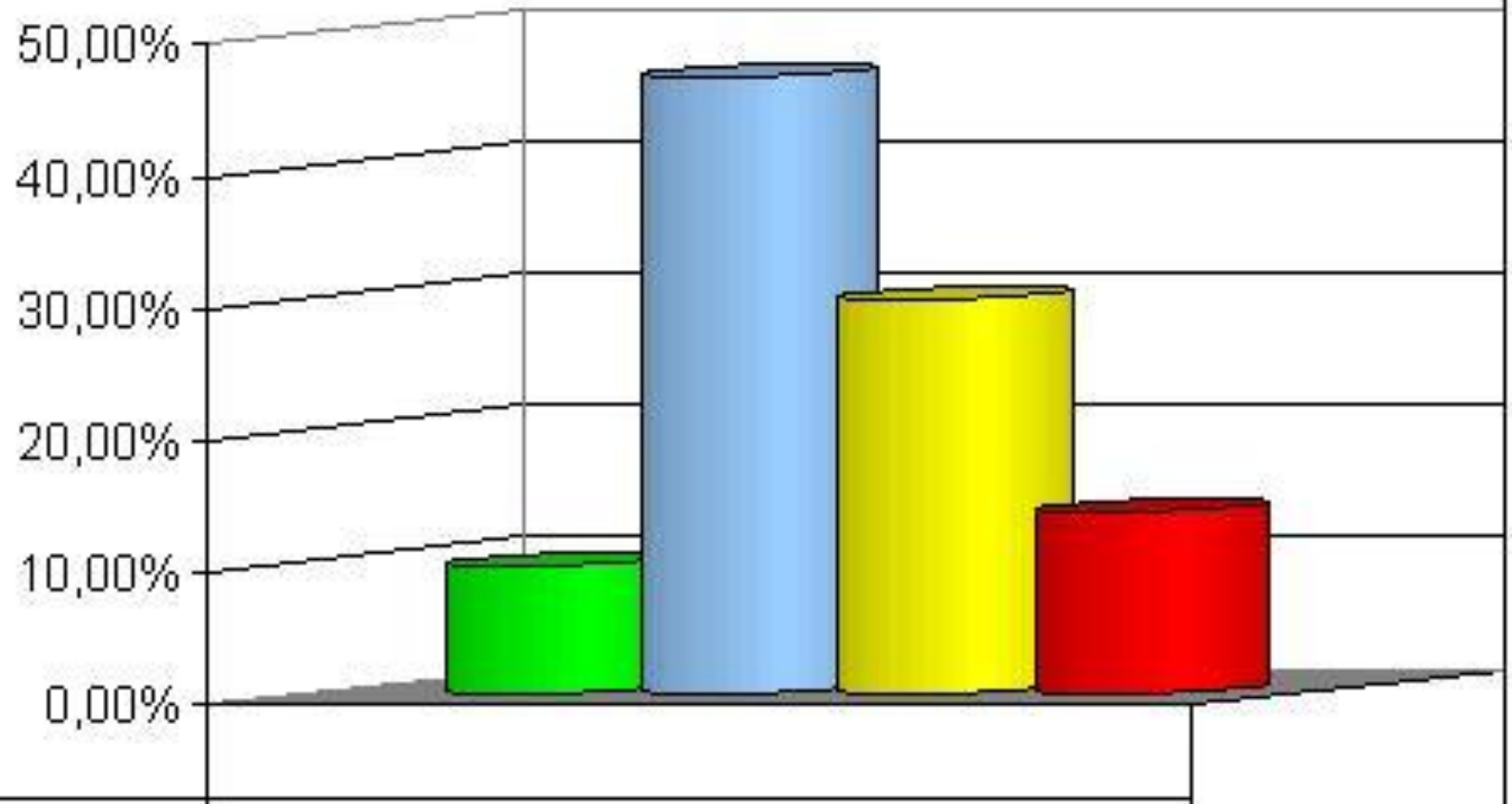
these certified by the experts of the Court of Lecce
provides an overall picture of the statistics

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

OVERALL RESULT

TOT	remission	regression	stability	progression
124	12	58	37	17

Results group B (n.124)



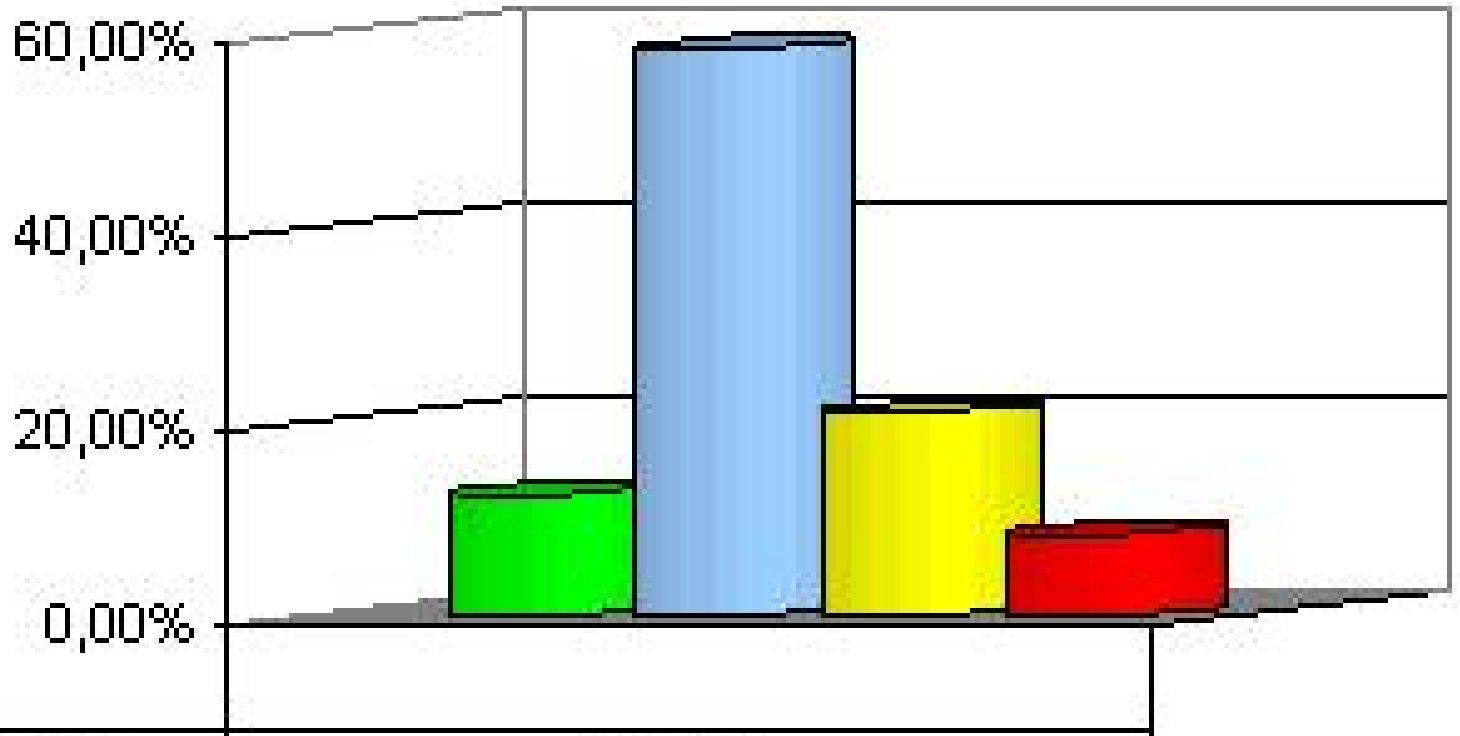
REMISSION	9,70%
REGRESSION	46,80%
STABILITY	29,80%
PROGRESSION	13,70%

Leukemia Lynf - 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)

LEUKEMIA-LYMPHOMA (n. 24 patients)



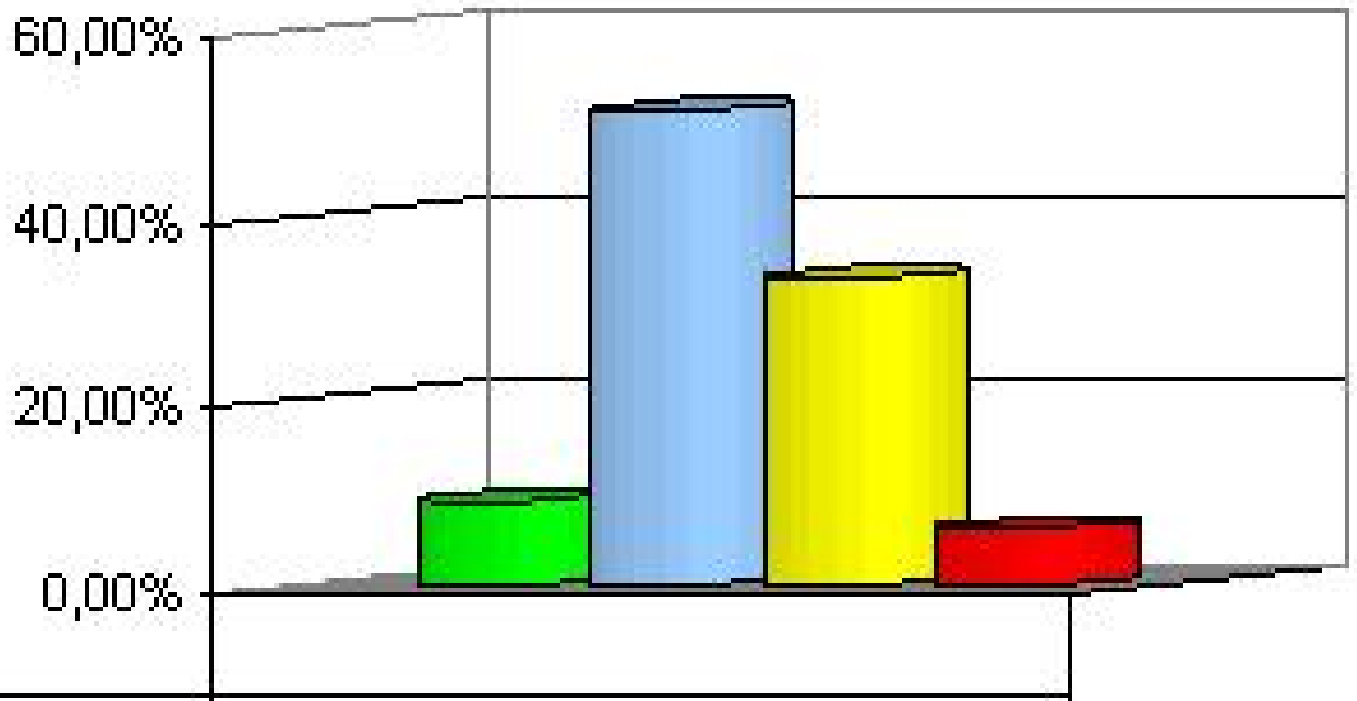
REMISSION	12,50%
REGRESSION	58,33%
STABILITY	20,83%
PROGRESSION	8,33%

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)

BREAST (n. 33 patients)

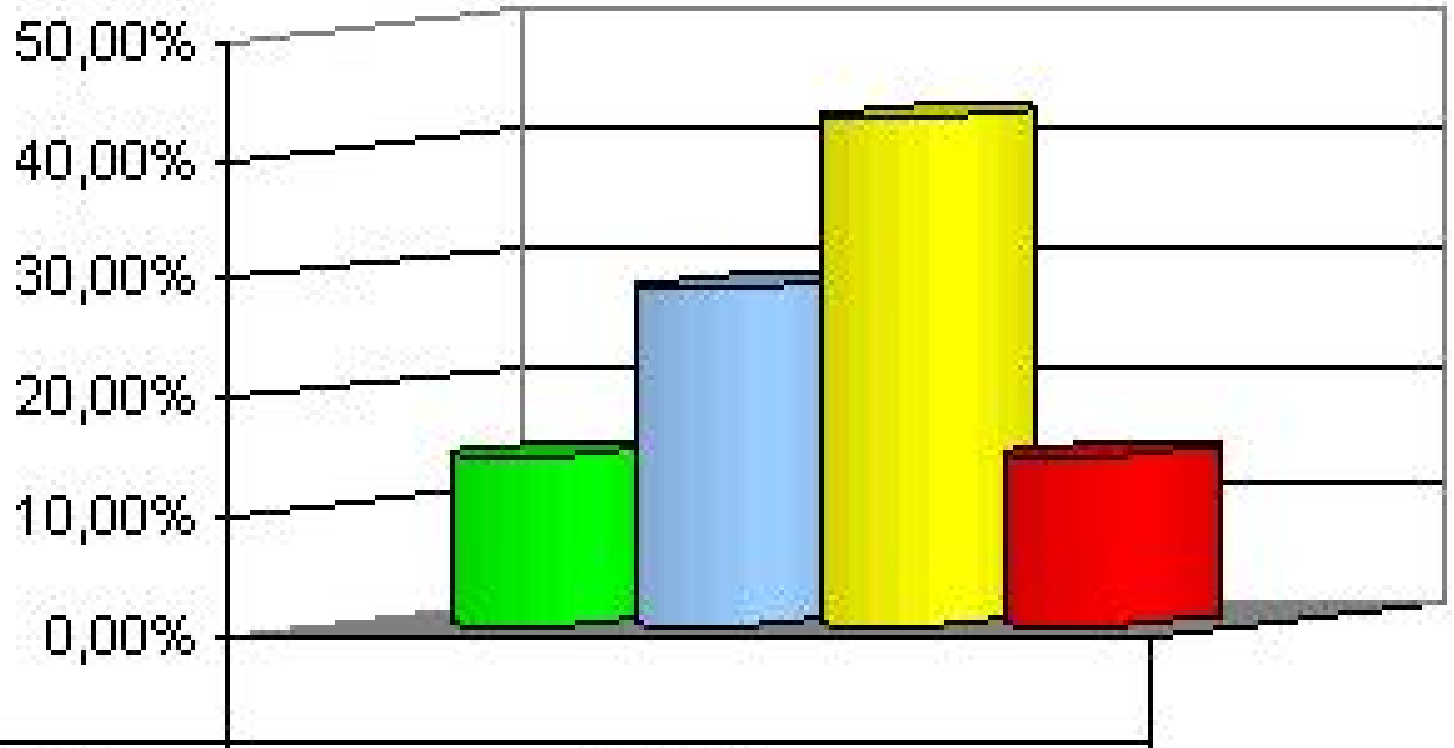


REMISSION	9,09%
REGRESSION	51,52%
STABILITY	33,33%
PROGRESSION	6,06%

Pancreas

TOT	remission	regression	stability	progression
7	1	2	3	1

PANCREAS (n. 7 patients)



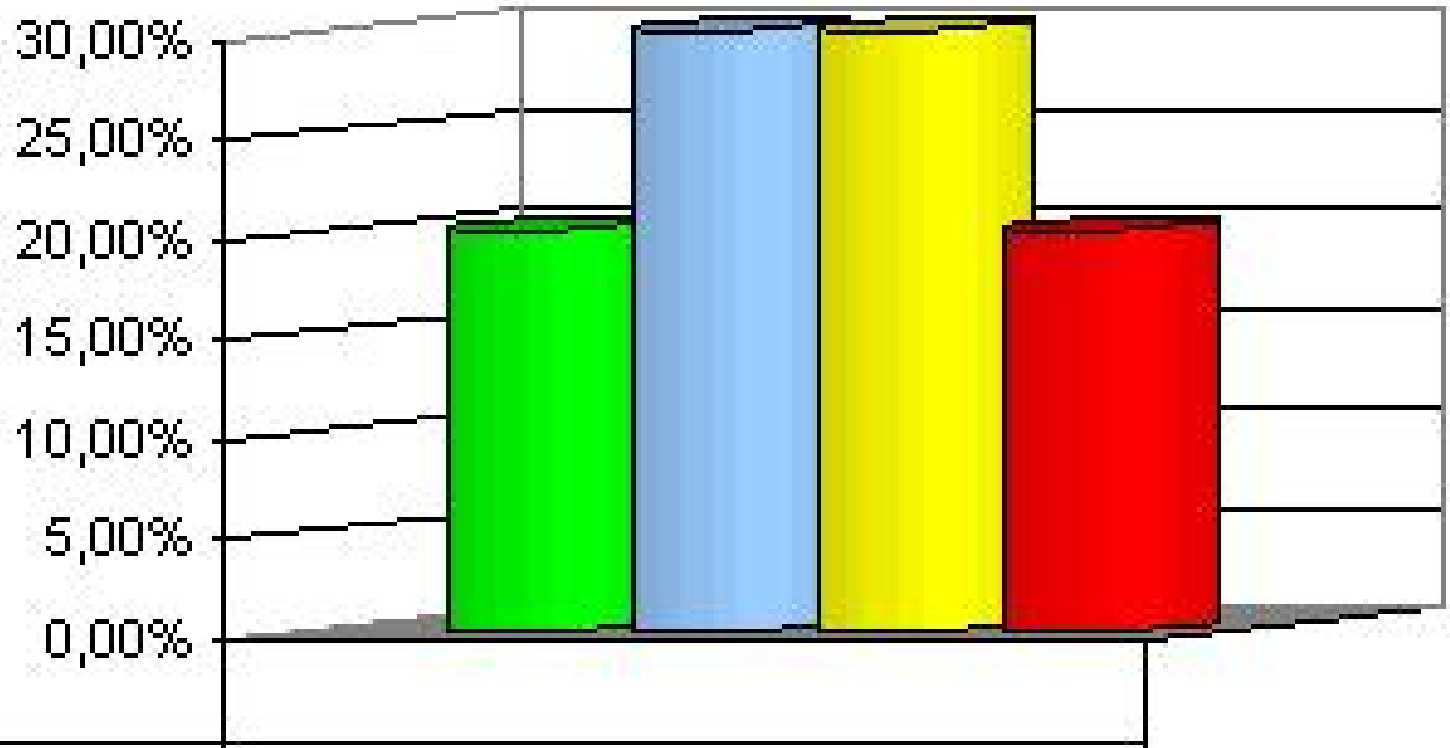
REMISSION	14,29%
REGRESSION	28,57%
STABILITY	42,86%
PROGRESSION	14,29%

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)

BRAIN (n. 10 patients)

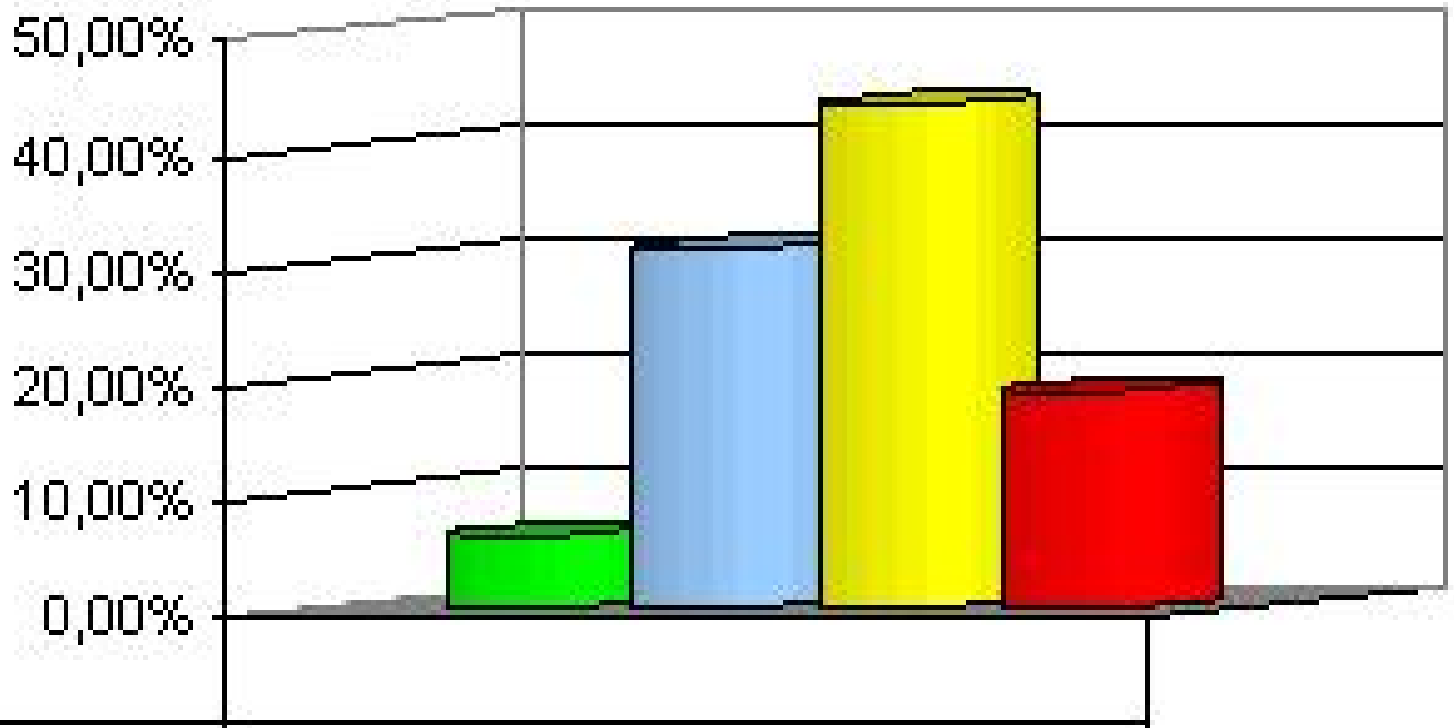


REMISSION	20,00%
REGRESSION	30,00%
STABILITY	30,00%
PROGRESSION	20,00%

Lung

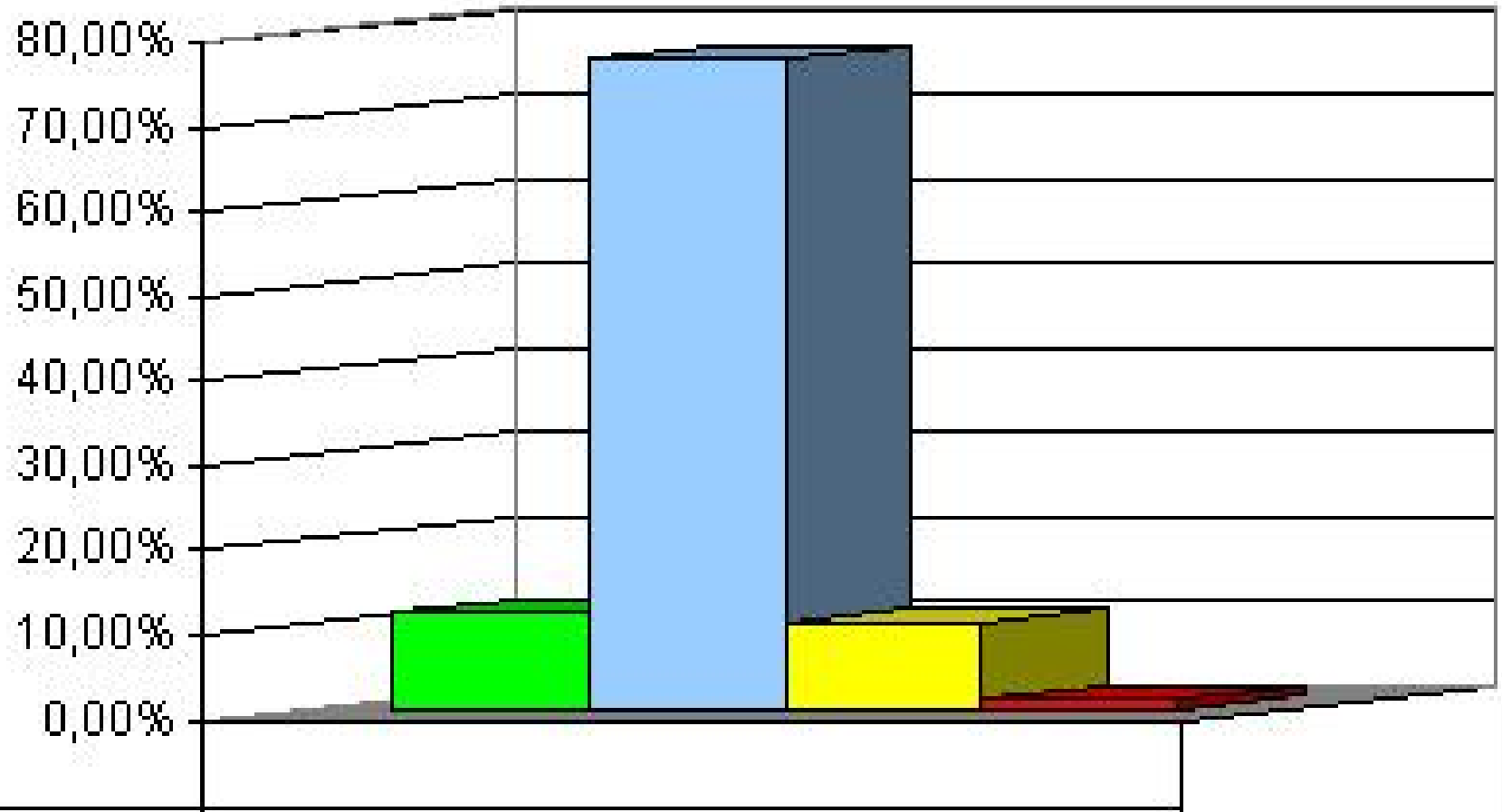
TOT	remission	regression	stability	progression
16	1	5	7	3

LUNG (n. 16 patients)



REMISSION	6,25%
REGRESSION	31,25%
STABILITY	43,75%
PROGRESSION	18,75%

PERFORMANCE STATUS



EXCELLENT	11,49%
GOOD	77,01%
SUFFICIENT	10,34%
BAD	1,15%

2)

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 NEL
1 case of cancer of the esophagus published in NEL
1 case of neuroblastoma published in NEL
74 cases of lung cancer published in Cancer Biotherapy,

3)

54 cases published in the Medical Journal Skepsis 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

4)

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

1 case of multiple myeloma	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 astrocytoma	1 case of pleomorphic liposarcoma
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 gastric lymphoma 1 case of non-small-cell pulmonary adenocarcinoma 1 case of epidermoid lung cancer
1 case of pleural mesothelioma	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
1 case of non-Hodgkin's lymphoma 1 case of cholangiocellular adenocarcinoma	Total: 125 cases
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	

5)

123 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: 123 cases

6)

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 have been published and are available on the Di Bella Foundation portal www.metododibella.org

7)

95th National Conference of the Italian Society

of Otorhinolaringology, Turin 2008

18 cases of head and neck cancer

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