The Di Bella Method (DBM) improved survival, objective response and performance status in a retrospective observational clinical study on 122 cases of breast cancer

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Abstract

OBJECTIVES: To increase the efficacy and reduce the toxicity of cancer therapy.
METHOD: The DBM with MLT, Retinoids, vitamins E, D3, and C has a differentiating, cytostatic, antiangiogenic, immunomodulating, factorially synergic effect, at the same time reinforcing those functions that Physiology considers essential for life. With Somatostatin and/or its analogues, the DBM has an antiproliferative effect, negatively regulating the most powerful mitogenic molecule (GH), receptorially co-expressed and interactive with Prolactin, inhibited by Cabergoline and/or Bromocriptin. The negative regulation of GH extends directly to the GH-dependent growth factors. In breast cancer, the DBM entails the use of estrogen inhibitors and minimal apoptotic, non-cytotoxic and non-mutagenic doses of Cyclophosphamide or Oncocarbide, the tolerability of which is enhanced by MLT and the vitamins in the DBM.
RESULTS: Complete and stable cure of 4 cases, and rapid regression of the tumour in another 5 cases with just the DBM (first-line therapy), without surgical intervention. No disease recurrence with the use of the DBM as adjuvant therapy. Five-year survival of 50%, of stage IV cases, considerably higher than the data reported in the literature. A more or less generalised improvement in the quality of life, without any significant and/or prolonged toxicity.
CONCLUSIONS: The acknowledgement of the still underestimated scientific evidence, such as the multiple antitumoral mechanisms of action of MLT, the negative regulation of the interactive mitogens GH–GF (GH-dependent growth factors), Prolactin and estrogens, together with the differentiating and homeostatic action of retinoids and Vitamins E, D3, and C and MLT, made it possible to achieve these results. An essential aspect of the mechanism of action on the clinical response is the factorial synergy of the DBM components.

CASE REPORTS

Abbreviations:

ATRA	- All Trans Retinoic Acid
DBM	- Di Bella Method
EGF	- Epidermal Growth Factor
EGFR	- Epidermal Growth Factor Receptor
ER	- Estrogen 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
NOSe	- Endothelial Nitric Oxide Synthase
PDGF	- Platelet-Derived Growth Factor
PET	- Positron Emission Tomography
PG2	- Prostaglandin 2
SST	- Somatostatin
SSTR	- Somatostatin Receptor
TGF	- Transforming Growth Factor
VEGF	- Vascular Endothelial Growth Factor
VIP	- Vasoactive Intestinal Peptide

METHOD

Active ingredients [components of the prescribed treatment (DBM)]:

1) Somatostatin (14 amino acids) 3–4 mg injected subcutaneously at night, to coincide with the night-time peak of incretion of GH, and over the space of 10 hours by means of a programmable timer (for the short half-life – approximately 3 minutes).

2) Octreotide, analogue of somatostatin (8 amino acids) in lag time formulation, 30 mg intramuscular, every 25 days, for complete receptor and temporal saturation, with the same antiproliferative and pro-apoptotoc properties as somatostatin with 14 amino acids.

3) Bromocriptin 2.5 mg tablets (1/2 tablet morning and evening), to inhibit prolactin, a powerful and ubiquitous mitogenic hormone, receptorially co-expressed with GH on the cell membranes and interactive with GH.

4) Cabergoline 1/2 tablet (twice a week), to reinforce the activity of bromocriptin, with a considerably longer half-life.

5) vitamin solution, according to Prof. Di Bella's formulation:

Beta carotene	2 g
Palmitate axerophthol	1 g
All-trans retinoic acid (ATRA)	1 g
Alpha-tocopheryl acetate	1 000 g

One dessertspoon (100 mg × kg of body weight), at least 15 minutes before eating, 3 times a day.

6) Dihydrotachysterol (synthetic Vit D_3) 10 drops in the same spoon together with the vitamin compounds (30 drops a day).

7) Melatonin, chemically complexed with adenosine (by means of a hydrogen bond) and glycine, from 40 to 60 mg a day according to Prof. Di Bella's formulation: Melatonin 12%, Adenosine 51%, Glycine 37%.

8) Aromatase inhibitor one tablet a day.

9) Hydroxyurea 500 mg tablets (1 tablet twice a day) , or **Cyclophosphamide** 50 mg tablets (1 tablet twice a day).

10) Calcium 1 g twice a day, with the ascorbic acid

11) Ascorbic acid 2 g together with the calcium in a glass of water (twice a day with meals).

12) Chondroitin sulfate 500 mg tablets (1 tablet twice a day).

CASE SERIES

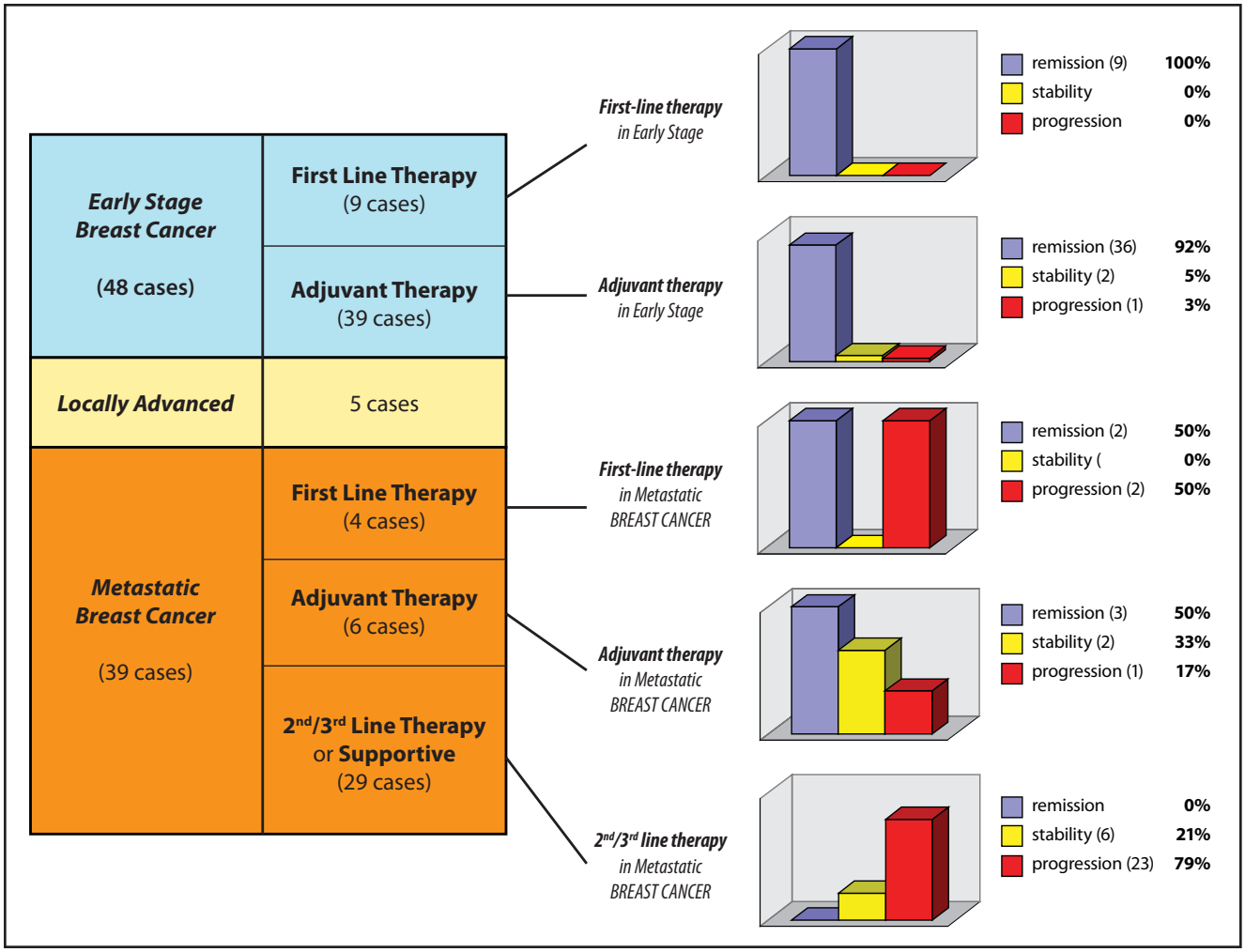
Results

This retrospective observational clinical study was performed by monitoring (92) cases of breast cancer treated with the DBM for at least five years. The monitoring consisted of all the elements necessary to process a statistical study aimed at correctly representing the clinical and therapeutic results achieved (survival, objective response, performance status).

Of these cases, *82%* were *infiltrating ductal tumours, 13%* were *infiltrating lobular tumours and 5% were other types*. Thirty other cases were also examined by experts and certified by the Court of Lecce (Italy). These 30 cases treated with the DBM showed a net improvement in objective response and quality of life after the failure of previous oncological treatments and, on the basis of the documented results, were awarded free prescription of the DBM drugs (not foreseen by the Italian NHS) by the Judicial Authorities. On the basis of the expert's report, the magistrate ruled that the Italian national health service was obliged to provide all the DBM drugs free of charge.

Aware of the limits that statistics assign to representations for limited numbers of cases, it must however be taken into account that not one but all the parameters for comparison with traditional treatments were decidedly surpassed (and by several percentiles), but above all for the first time a series of cases showed complete and permanent cure, without the help of previous treatment, be they pharmacological, radiation or surgical.

Tab. 1. Classification and subdivision of the cases.



In terms of five-year survival, the DBM achieved markedly superior results, for each stage, compared to those reported by the National Cancer Institute (N.C.I) in the 12 SEER, Areas project.

Classification and subdivision of the cases (Table 1)

Of the 122 cases:

Group A) 48 were in the early stage, of which
A/1) **9** followed the DBM as first-line therapy
A/2) **39** followed the DBM as adjuvant therapy

Group B) 39 were in the metastatic stage, of which
B/1) **4** of these had not had any medical treatment (DBM as first-line therapy)
B/2) **6** of these had previously been treated with surgery (DBM as adjuvant therapy)
B/3) **29** cases underwent surgery and chemotherapy and/or radiation therapy
(DBM as 2nd/3rd line or supportive therapy)

Group C) 5 cases started the treatment in a locally advanced situation

Group D) 30 cases certified by the Court of Lecce (Italy)

Data analysis

Group A) Early Stage Breast Cancer (48 cases)

A/1) DBM as First-Line Therapy (9 cases)

Nine patients with stage I-II-IIIa breast cancer refused surgery and chose the DBM as the only treatment. Four out of the nine cases achieved complete remission; three of these have been disease-free for over 48 months and one for 63 months (Table 2). The other five are still undergoing treatment, with a progressive and evident reduction in the size of the tumour (Figure 2).

A/2) DBM as adjuvant therapy (post-surgery – 39 cases) (Figures 3–5)

In 39 cases, the MDB was used as adjuvant therapy with a marked and significant increase in Overall Survival (median at 60 months = 100%) and disease-free period.

At entry in the therapeutic trial, 12 patients presented evident signs of disease recurrence (local or lymph nodes). As far as efficacy is concerned, the

results achieved were significant: 95% remission (all currently disease-free; five-year survival 100%).

Only one patient showed signs of progression, 2 years after suddenly discontinuing the treatment on her own initiative.

Comparison of the 100% five-year survival results achieved with the DBM with the official survival medians obtained with the following protocols and chemotherapy combinations :

TAC = Taxotere + doxorubicin + cyclophosphamide
FAC = Fluorouracil + doxorubicin + cyclophosphamide

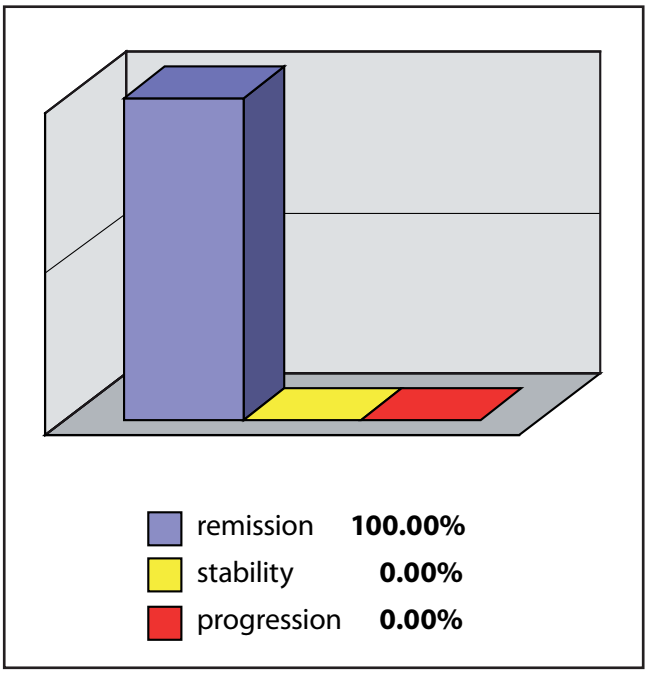


Fig. 1. Effectiveness as first-line therapy.

Tab. 2.

ARCH.	ST.	INITIAL CONDITION	OUTCOME	CURRENT CONDITION
601	I	Right breast multifocality (1.5 cm – 1 cm) + 2 small brain lesions of uncertain nature	Full Remission	Absence of Disease
1941	II A	Bilateral lesions - negative biopsy after 6 months DBM treatment	Full Remission	Absence of Disease
138	II A	Left breast multifocality and 2 reactive lymph nodes	Full Remission	Absence of Disease
1101	II B	2 nodules in right breast (2 cm) + positive lymph node	Full Remission	Absence of Disease
614	II A	2.5 cm mammary carcinoma + lymph node	Partial Remission	Nodule reduction/ Lymph nodes disappeared
2178	II A	2 cm nodule - lymphadenopathy	Partial Remission	PET scan shows small residual in mammary area
657	II A	3.5 mm nodule	Partial Remission	12 mm nodule reduction
2898	I	16 mm nodule	Partial Remission	5 mm nodule
2708	II B	6.3 × 3.6 × 3.9 cm lesion (Figure 2)	Partial Remission	Significant reduction (90%)

Group B) Metastatic Breast Cancer (39 cases, Figure 6)

B/1) DBM as First-line Therapy (4 cases, Table 3)

DBM as first-line therapy (without surgery): a total of 4 cases (2 remissions – 2 progressions)

One of these who showed lymph nodal, retropectoral and bone metastases (Arch. No. 994) had evident partial remission; she is still alive with a good quality of life and, apart from the bone metastases, the other sites are in remission. Another case (Arch. No. 586), with 2

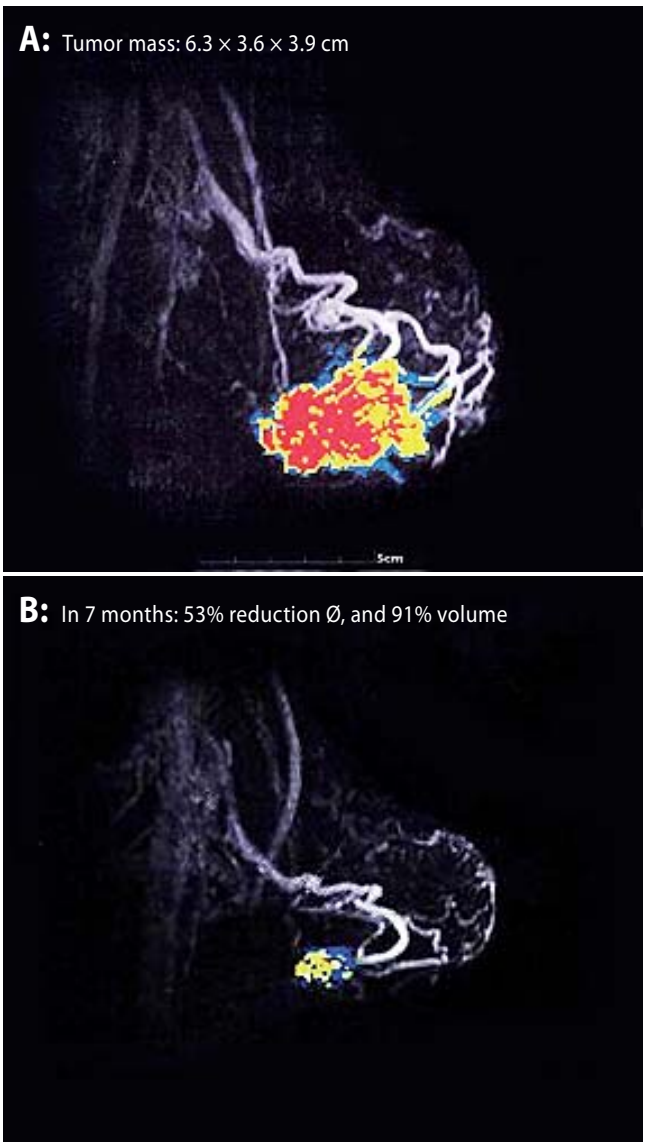


Fig. 2. Arch. no. 2708. The inhibition of angiogenesis induced by SST, cabergoline, and bromocriptine is synergistically enhanced by MLT, retinols, vit. D3, E, C. The same differentiating and apoptotic molecules (melatonin, retinoids, vitamins C, D3, and E) combined with minimal doses of chemotherapy, causes a slow but progressive reduction of the neoplastic concentration, determining significantly objective results, until complete remission (MRI-CAD Stream).

nodules in the right breast and lung metastases, is in remission and still living 56 months later.

B/2) Previously treated with surgery (DBM as adjuvant therapy) – 6 cases (Table 4, Figure 7)

DBM as adjuvant therapy: a total of 6 cases (3 remissions – 2 stable – 1 progression)

Six underwent surgery but not chemotherapy and the DBM was therefore used as adjuvant therapy. Five of these patients are alive; one with lung and lymph node metastases (Arch. No. 1826) had complete remission, one (Arch.No. 2440) with axillary infiltration and widespread bone metastases had very evident partial remission (Figure 7) as did another case with liver and bone metastases (Arch. No. 2726). One case of lung, bone and lymph node metastases is stable, as is another case with multiple bone metastases. The last case with metastases in 30 out of 32 lymph nodes and widespread bone metastases died after 38 months.

(Arch n. 2440: a patient who underwent surgery but not chemotherapy, treated with adjuvant DBM)

B/3) DBM as 2nd/3rd line or supportive therapy [29 cases (6 stable – 23 progressions)] (Figure 8)

Patients who had previously undergone chemotherapy and surgery (now therapy orphans).

General data: net and significant improvement in Overall Survival (39 patients).

Survival median = 18 months (30% of the patients are alive at 30 months) compared to the results obtained at the same stage with various chemotherapy protocols .

Group C) Locally Advanced Breast Cancer Stage III b-c (5 cases) (Table 5, Figures 9–10)

Two significant results were observed among these five cases: the survival, after 60 months, of one patient with complete remission of a voluminous infiltrating ductal carcinoma (Arch. No. 688) which, when treat-

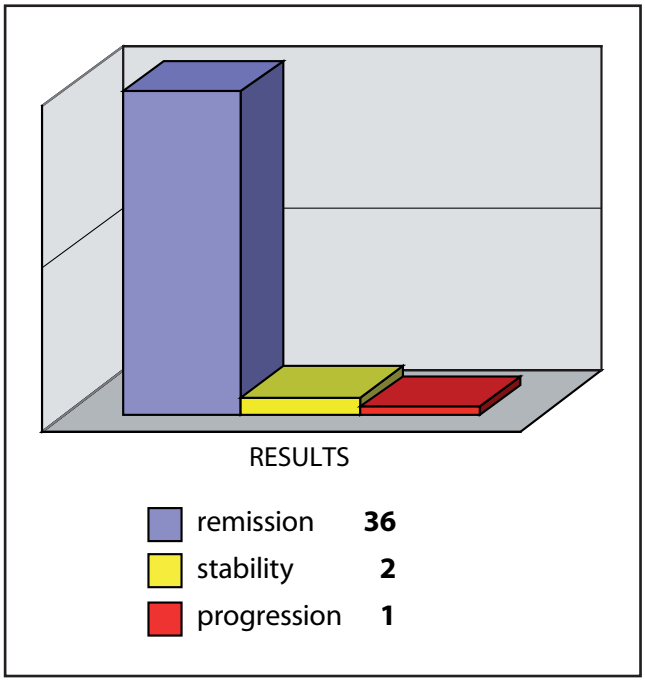


Fig. 3. Overall effectiveness - DBM as adjuvant therapy in Early Stage – 39 cases.

Tab. 3.

ARCH.	INITIAL CONDITION	OUTCOME	CURRENT CONDITION	SURVIVAL
994	Lymph nodal - retro-pectoral -medi astinic - bone metastases	Partial Remission	Remission everywhere except bone	22 months - living
586	2 nodules in right breast + lung metastases	Remission	Living	56 months - living
970	Advanced stage bilateral carcinoma - several bone and lunq metastases	Progression	Dead	17 months
2224	Axillary, breastbone and bone recurrence	Progression	Slow progression	19 months - living

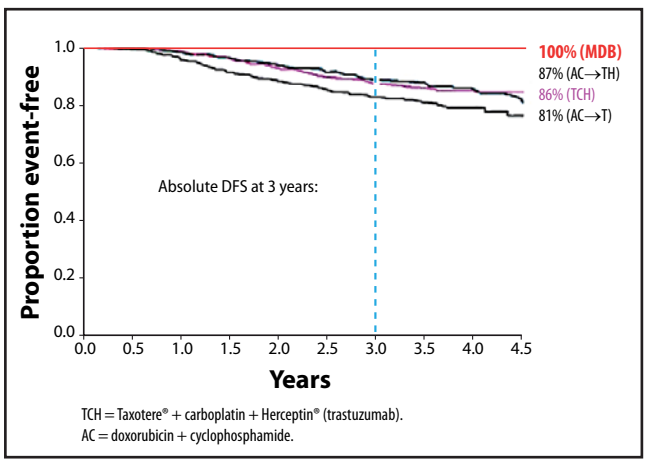


Fig. 4. Free Disease Survival - DBM as adjuvant therapy in Early Stage – 39 cases.

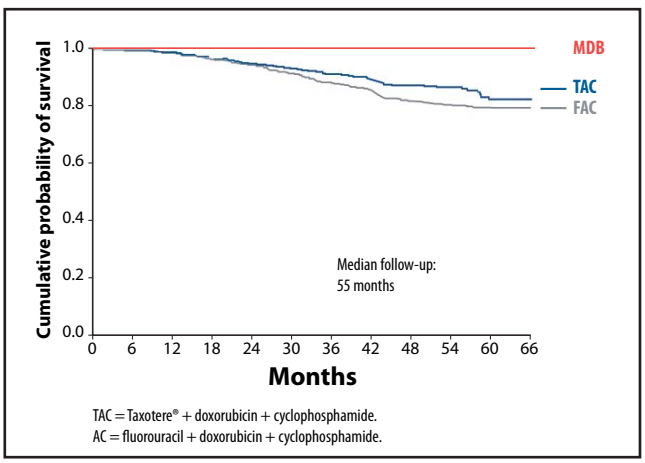


Fig. 5. Five-year-Survival - DBM as adjuvant therapy in Early Stage – 39 cases.

ment was started, presented a lung progression, and the stability of another patient with another voluminous tumour surgically removed (Arch no. 1638) who is still alive at 28 months.

In the comparison between the DBM and the data of the NCI 12 SEER Areas 1988–2001 project relative to five-year survival, while the data at stage III are more or less identical, the DBM achieves improvements at every other stage, with a particularly evident difference at stage IV, with 50% compared to the NCI's figure of 14.8%.

Tab. 4.

ARCH.	INITIAL CONDITION	OUTCOME	CURRENT CONDITION	SURVIVAL
1826	Lung metastasis + lymph nodes	Full Remission	Absence of Disease	27 months - living
2440	Axillaiy infiltration + widespread bone metastases	Partial Remission	Reduction in bone lesions	15 months - living
2726	Liver and bone metastases	Partial Remission	Reduction in metastases	12 months - living
1865	Lung + bone + lymph node metastasis	Stability	stability	26 months - living
2287	Multiple bone lesions	Stability	stability	18 months - living
1185	Metastases affecting 30 lymph nodes out of 32 + bone metastases	Progression	dead	38 months

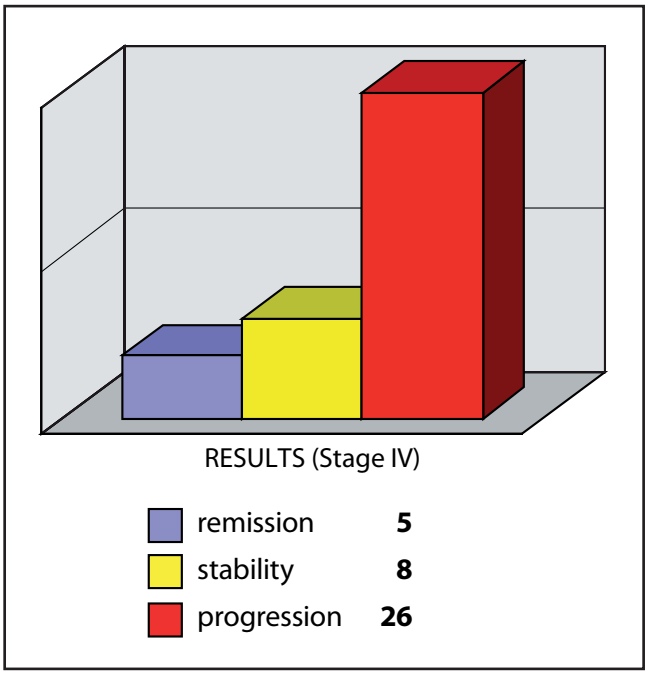


Fig. 6. Overall effectiveness in Metastatic Breast Cancer.

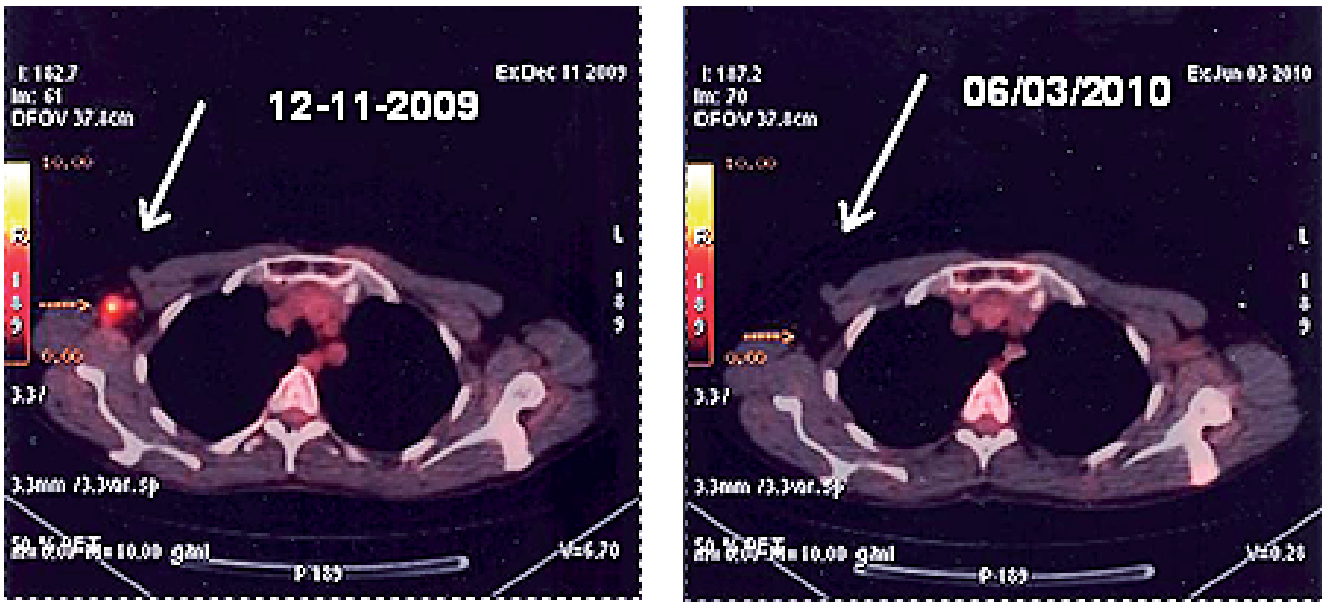


Fig. 7. Arch n. 2440: a patient who underwent surgery but not chemotherapy, treated with adjuvant DBM).
The patient underwent mastectomy in 1997 due to "Infiltrating ductal G2".
October 27, 2009 - Lymph node histological test "Infiltation due to ductal cancer, metastatic"
December 11, 2009 - PET scan: "... High metabolic activity lesions at axillary lymph nodal and bone level (dorsolumbar rachis, right acromion, some ribs bilaterally, right and left iliac regions, right pubic symphysis, left intertrocanteric region). Doubts with respect to right lung."
December 29, 2009 - start of DBM treatment
June 3, 2010 - PET scan "disappearance of the tracing focal hyper accumulation in the right nodal axillary region and some uptake skeletal areas (III front right costal arch, IV back right arch, left iliac ala, right sacroiliac synchondrosis and left intertrochanteric region) uptake gradient reduction at a vertebral level, uptake gradient reduction in the right subareolar region"

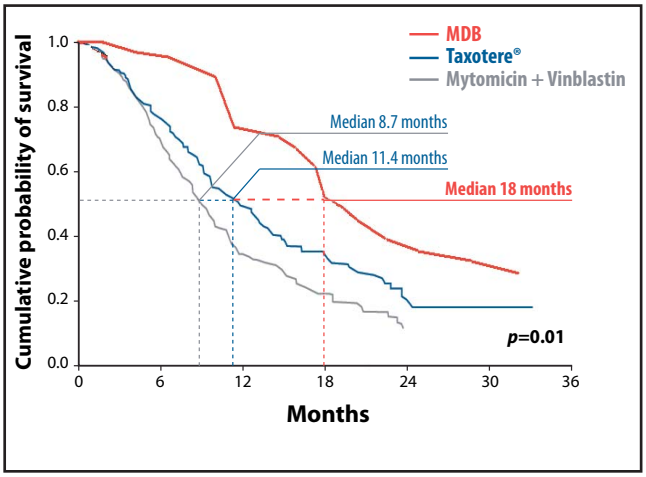


Fig. 8. Probability of survival in Metastatic Breast Cancer.

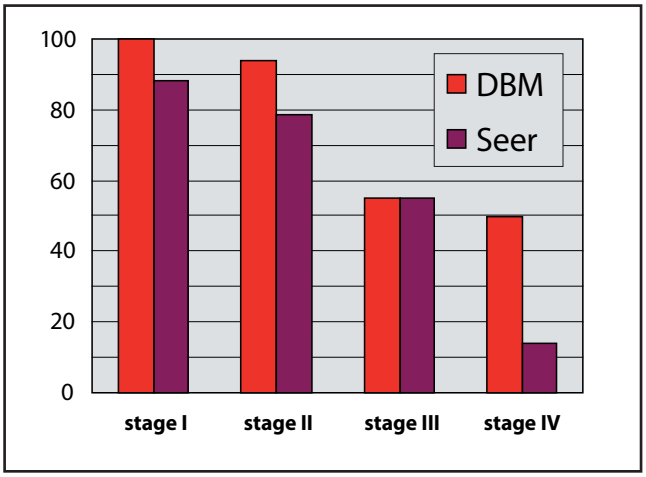


Fig. 9. Comparison DBM-NCI.

Tab. 5.

ARCH.	INITIAL CONDITION	OUTCOME	CURRENT CONDITION	SURVIVAL
799	Advanced stage - inoperable	Progression	Likely to be dead (not possible to get in touch with her)	16 months (at least)
2680	(morphine) - widespread metastases affecting subclavian-neck and axillas lymph nodes	Progression	Dead 7/2010	7 months
895	Breast carcinoma 5 cm + lymph nodes	Progression (incomplete treatment)	Dead 2/2008 (pneumonia)	5 months
688	1 lung nodule	Full remission	No illness	60 months alive
1638	After surgery treated for prevention	Stability	Without changes	28 months alive

RATIONALE OF THE THERAPY

More detailed studies have recently been performed to confirm the known molecular mechanisms of the mitogenic role of GH (Milewicz 2011; Chiesa 2011) and of prolactin (Aksamitiene 2011), whose membrane receptors are co-expressed and interactive (Chen 2011; Breves 2011; Xu 2011). It has also been confirmed that the receptors of Somatostatin and Dopamine functionally interact with an antiproliferative effect (Diakatou 2011; Savenau 2011; Ferone 2010; Gruszka 2001). The ubiquitary receptorial expression of prolactin (Sandret 2011; Ben-Jonathan *et al.* 2002; Hooghe *et al.* 1998) and of GH (Taboada 2010; Lincoln *et al.* 1998; De Souza *et al.* 1974) confirm the mitogenic role of these molecules. This is also confirmed in breast cancer (Wennbo *et al.* 2000). The causal and proportional relationship between the receptorial expression of GH (of which SST is the biological antidote) and tumoral induction and progression (Friend *et al.* 2000; Zeitler *et al.* 2000; Gruszka *et al.* 2001) has also been shown, histochemi-

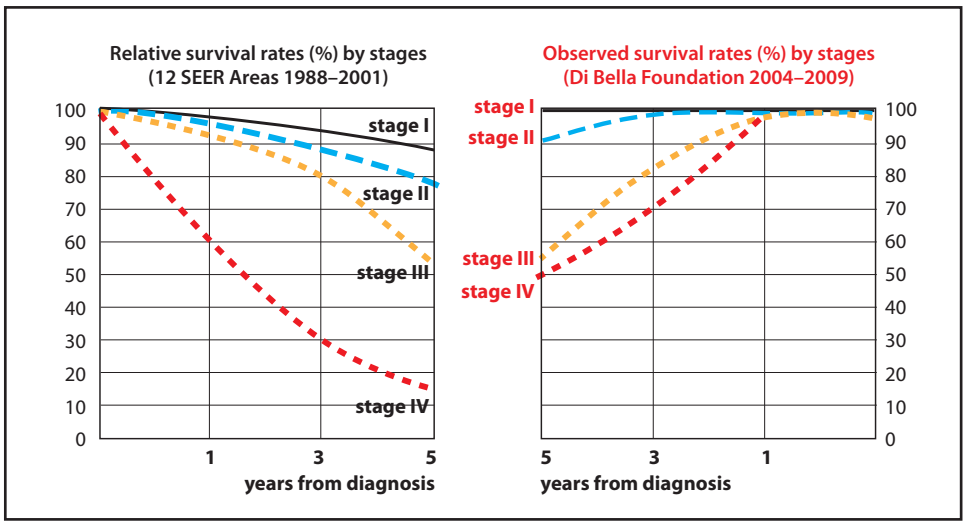


Fig. 10. Comparison DBM-NCI.

cally demonstrating much higher concentrations of GHR in tumour tissues with respect to healthy tissues. There are numerous confirmations that the inhibition of GH exerts an antiproliferative effect (Bustamante 2010) and the administration of GH therefore represents a high risk of tumour induction (Sklar 2004). The powerful mitogenic role of GH is therefore known and well documented, as is the fact that the proliferative index and the speed at which the tumour populations progress are directly proportional, in a dose-dependent way, to the receptorial expression of GH (Lincoln *et al.* 1998).

Cell proliferation also strictly depends on GH-dependent mitogenic molecules positively regulated by GH, such as EGF, FGF, HGF, IGF-1-2, NGF, PDGF, VEGF, TGF, and HGF (Yarman 2010; Hagemeister *et al.* 2008; Taslipinar *et al.* 2009; Di Bella 2004; 2008; 2009; 2010; Murray *et al.* 2004; Sall *et al.* 2004; Szepesházi *et al.* 1999) as well as on growth factors produced by the gastrointestinal system, such asVIP, CCK, and PG (Kath *et al.* 2000).

Both physiological and neoplastic cell proliferation is triggered by these same molecules, which the tumour cell thus uses exponentially compared with a healthy cell. Biological antidotes of GH, such as Somatostatin and its analogues, not only reduce the plasma rate of GH, but also the expression and transcription of highly mitogenic growth factors, such as IGF1-2 (Cascinu *et al.* 2001; Pollak 1997; Schally *et al.* 2001), EGF (Held-Feindt *et al.* 1999), and FGF (Mentlein *et al.* 2001), and extend their negative regulation to the respective receptors with evident antiproliferative and antiangiogenic repercussions (Szepesházi *et al.* 1999; Mishima *et al.* 1999; Barrie 1993).

It is known that the interaction of GH–PRL with the GH-IGF axis and the PRL–IGF axis has a determining influence on biological neoplastic development.

Evidence is now emerging on the interaction between estrogen and IGF, and thus on the central function of IGF as a common proliferative modulator of GH, PRL, and estrogen. The estrogen-IGF axis is involved in mastoplasia and in breast cancer (Kleinberg 2010), and interacts blastically with other endocrine systems like GH–IGF–PRL (Lynn 2011; Zhou 2011; Mendoza et al 2010; Hewitt 2010; Leung 2004; Fürstenberger 2003; Juul 2001; Lissoni 1987; Mauri 1985). The interaction of these mitogenic endocrine systems confirms the rationale of the DBM which envisages the simultaneous and synergic inhibition of GH, PRL, and estrogen and, consequently, of IGF in breast cancer with or without ascertainment of the expression of ER. Our clinical results on the 122 cases monitored confirmed the scientific and rational grounds of this therapeutic concept. IGF receptors which respond mitogenically to the ligand were detected not only in breast cancer, but also in a very high subtotal percentage of type of tumour cells. Somatostatin exerts its antiblastic activity both directly, by inhibiting the expression of the IGF gene, and indirectly, by suppression of GH, on which the incretion of IGF depends (Pollak 1997; Schally *et al.* 2001; Schally *et al.* 2003). There is also considerable evidence of the inhibitory activity of SST on another powerful mitogenic growth factor, EGF, frequently expressed in breast cancer, through multiple mechanisms:

- dose-dependent inhibition of the tyrosine phosphorylation induced by the activation of EGFR by EGF (Mishima *et al.* 1999);
- reduction of EGFR in the tumour cells (Szepesházi *et al.* 1999);
- reduction of the expression of EGF (Held-Feindt *et al.* 1999);
- decrease of the plasma concentration of EGF (Cascinu *et al.* 2001).

Mitogens produced by the gastrointestinal system, such as VIP, CCK, and PG, are strongly inhibited by somatostatin and/or octreotide (Kath *et al.* 2000).

It has been demonstrated that breast tumours express SSTR1, SSTR2, SSTR3, and, less frequently, SSTR5 (Albérini *et al.* 2000; Schaer *et al.* 1997), which in at least 50% of cases are scintigraphically visible, while in more than half of negative scintigraphs histochemical analyses have revealed the presence of SSTR. The presence of SSTR (Albérini *et al.* 2000; Barnett *et al.* 2003; Pinzani *et al.* 2001; van Eijck *et al.* 1998) and of neuroendocrine receptors in a significant percentage of these tumours therefore represents an additional rational indication for the use of SST, already amply justified by the aforementioned negative regulation of SST on GH, GH-correlated oncogenes, and angiogenesis.

Promoters of angiogenesis, an essential phase of tumour progression, such as monocyte chemotaxis, IL8, PG2, and NOSe, as well as the contribution of growth factors (whose synergism is essential for angiogenesis), such as VEGF, TGF, IGF1, FGF, HGF, and PDGF, are negatively regulated by Somatostatin and its analogues (Albini *et al.* 1999; Barrie *et al.* 1993; Cascinu *et al.* 2001; Florio *et al.* 2003; Jia *et al.* 2003; Turner *et al.* 2000; Vidal *et al.* 2000; Watson *et al.* 2001; Wiedermann *et al.* 1993).

The inhibition of angiogenesis induced by SST is synergically reinforced by other components of the DBM, such as MLT (Lissoni *et al.* 2001; Di Bella *et al.* 1979; Di Bella *et al.* 2006), Retinoids (McMillan *et al.* 1999; Kini *et al.* 2001; Majewski *et al.* 1994), vit. D_3 (Kisker *et al.* 2003; Mantell *et al.* 2000), Vit. E (Shklar *et al.* 1996; Tang *et al.* 2001; Neuzil *et al.* 2002), vit. C (Ashino *et al.* 2003), prolactin inhibitors (Turner *et al.* 2000), and components of the extracellular matrix (Liu *et al.* 2005; Ozerdem *et al.* 2004) .

The cytostatic, antiproliferative, and antimetastatic effect of Somatostatin is also effectively synergised by the other components of the DBM:

- Retinoids (Hassan *et al.* 1990; Voigt *et al.* 2000; Piedrafita *et al.* 1997; Onogi *et al.* 1998).
- MLT (Bartsch C *et al.* 1999; Kvetnoĭ IM *et al.* 1986; Mediavilla MD *et al.* 1999; Maestroni GJ *et al.* 1996; Cos S *et al.* 2000)

- Vit D_3 (Jensen SS *et al.* 2001; Barroga EF *et al.* 2000; Campbell MJ *et al.* 2000)
- Cabergoline and Bromocriptin [prolactin inhibitors] (Gruszka *et al.* 2001; Ben-Jonathan *et al.* 2002; Lissoni *et al.* 2001; Klijn *et al.* 1996; Manni *et al.* 1989)
- Galactosamine sulfate, components of the extracellular matrix (Pumphrey *et al.* 2002; Batra *et al.* 1997)
- Vit E (Turley *et al.* 1995; Israel *et al.* 2000; Malafa *et al.* 2002; Neuzil *et al.* 2002; Shklar *et al.* 1996)
- Vit C (Head 1998; Murata *et al.* 1982; Cameron *et al.* 1979)

The growing interest in the antitumoral properties of MLT which Prof Luigi Di Bella was the first to use in 1969 in solid tumours, in leukaemia and in diseases of the blood (Di Bella 1974, 1976, 1979, 1980, 1988, 1994, 1996, 1998) is documented by the continuous increase in publications and by the growing development of this line of research. The recent publication on the DBM (Di Bella 2010) reported numerous indications of its differentiating and antiproliferative action, and the receptorial expression of the cytosol and nuclear membrane of MLT, together with the receptorial synergism with RAR and RXR of the retinoids, and VDR of vitamin D. There is growing confirmation of Prof Luigi Di Bella's intuition in defining MLT as a necessary, albeit not sufficient, component in the treatment of cancer (Hill 2011; Korkmaz 2009, Benitez-King 2009; Cabrera 2010; Cucuna 2009; Dong 2010; Girgert & Lin 2010; Mao 2010; Mediavilla 2010; Rogelsperger 2009).

In addition to inhibiting neoplastic proliferation, the strategic objectives of an antiblastic treatment must include control of 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 and, as they progress, they follow a predefined programme of survival inherited from bacteria (Radman *et al.* 1975) (transferred by the 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 (Israel 1996).

The paper mentioned above (Di Bella 2010) described the Di Bella Method in greater detail, reporting the homologies between the proteins and genes of the bacterial "SOS" system and those contained in our cells. In the May 2011 edition of Nat Rev Cancer, the article by Lambert *et al.* entitled "An analogy between the evolution of drug resistance in bacterial communities and malignant tissues" discussed and confirmed what I reported in Neuroendocrinology Letters (2010; 31Suppl 1: 1–42) in the paper entitled "The Di Bella Method (DBM)". These studies provide greater awareness of the fact that 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 with differentiating and antiproliferative molecules, 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.

CONCLUSIONS

These results are proof of the rationality and efficacy of the multitherapy conception of the DBM which, through the synergic integration of its components, upholds and enhances the vital reactions and antitumoral homeostasis to enable them to counter the onset and progression of the tumour by means of:

a. defence against the neoplastic aggression
b. inhibition of neoplastic **proliferation**
c. contrasting the marked mutagenic tendency of the neoplastic phenotype.

The tumour is a deviation from normal life, making it necessary to restore the altered reactions to normal by reinforcing all the means that Physiology considers essential for life.

The documented antiangiogenic synergism of every component of the DBM, together with the antiproliferative effect of somatostatin, and prolactin and estrogenic inhibitors, and the differentiating, immunomodulating, trophic and homeostatic effect of the other components have achieved a significant result from various points of view: the complete, stable and objective response in several patients without the need for surgery, the particularly significant increase in the median of five-year survival of stage IV cases, a generalised and marked improvement in the quality of life, and transitory and mild side effects which could be easily controlled and which were absolutely irrelevant if compared with the known toxicity of chemotherapy.

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