

# Complete objective response, stable for 5 years, with the Di Bella Method, of multiple-metastatic carcinoma of the breast

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## Abstract

Breast cancer is the most common cancer and the leading cause of cancer death among women. Despite all efforts, about 11,939 deaths and 50,000 new diagnoses for breast cancer were estimated among Italian women in 2016. Therefore new approaches are needed to improve the survival and higher remission rates. We present a case of a woman with carcinoma of the breast and multiple metastases after right mastectomy, axillary dissection, repeated cycles of chemo and radiotherapy, and estrogen block. Biological method formulated by Prof. L. Di Bella (DBM) produced a complete and stable objective response without toxicity. The DBM includes antiproliferative molecules, such as somatostatin, prolactin and estrogen inhibitors together with differentiating and apoptotic molecules such as melatonin (MLT), Retinoids, Vitamin E, D3, Vit. C, Calcium, Amino sugars, associated with metronomic microdoses of chemotherapy drugs. The blood tests did not show any damage but a progressive reduction of Prolactin, Estradiol, and IGF1, and continuing low levels of GH. The objective result of this case, in the absence of toxicity, demonstrates the efficacy of the treatment and is in agreement with the positive results already published on the use of the DBM. Not requiring hospital or day hospital admission, and with no significant toxicity, the DBM avoided the significant side effects of chemo- and radiotherapy. We believe that this case can encourage more interest and more in-depth studies on the possibilities that have been opened up in oncology by the DBM treatment of the metastatic breast cancer.

## INTRODUCTION

The estimate in Italy dating year 2016, shows 50,000 new cases of breast cancer confirming that this type of tumour is the most diagnosed in woman. In 2013, the breast cancer represented the first absolute cause of death in all the world

for tumour in woman, with 11,939 deaths (Fonte ISTAT 2016). Breast cancer features 29% of death cause before 50 years old, 21 % between 50 and 69 and 16 % after 70 years old. The survival at 5 years is 85.5% in Italy, little bit more than the percentage in Europe ( 84.7%). (I numeri del cancro in Italia, 2016)

Current approaches could be different and depend from the type of cancer. The procedure includes conservative or radical surgery (mastectomy) associated with radiotherapy and/or chemotherapy, which also have variations according to the type and stage of the cancer (I numeri del cancro in Italia, 2016).

## CASE REPORT

We present 35-year-old woman with carcinoma of the breast detected during pregnancy, terminated at the 34th week of gestation by Cesarean section due to the diagnosis of the breast carcinoma. After the needle biopsy which showed an infiltrating carcinoma (G2), the patient underwent right mastectomy with axillary dissection and plastic reconstruction on 03.12.2009. Histological examination showed: *"Ductal carcinoma with an intermediate degree of differentiation, solid type intraductal focal component and widespread peritumoral vascular invasion. Tumor-free mammary parenchyma, with gravidic type modifications. Duct intraepithelial neoplasia areas (DIN2) with extension to the retroareolar ducts and extending close to the retroareolar margin. Lymph node: peri lymph node metastases of carcinoma with two sentinel lymph nodes and one II level lymph node. Histiocytosis of the breasts in the remaining twenty-four lymph nodes examined", and pT2 staging (2.5cm) pN1a(3/27) MX G2. Extensive vascular invasion; ER 90%, PgR 10%, Ki67 15%", c-erbB2: weak complete in 70%."*

The patient underwent 4 cycles of AC protocol chemotherapy and hormone therapy with Decapeptyl (3.75 mg/month) + Tamoxifen (20 mg die). A PET/CT scan performed on 10 May 2010 showed splenic uptake, confirmed by a subsequent abdominal ultrasound scan showing a small echo-poor area measuring approx. 8 mm at the top of the spleen. The CT scan performed on 26 May 2010 showed multiple solid lesions of the spleen (Figure 1). In April 2011,

the patient underwent mammary extensor replacement with prosthesis and left reductive mastoplasty. At the control MRI in May 2011, no progression of splenic lesions was showed, however ultrasound and mammography showed retraction, probably surgical, on the right side which needed further investigation. Abdominal ultrasound scan performed in November was negative. Blood tests performed in April 2012 showed an increased level of the Ca15.3 equal to 35.6; the patient thus started a series of specific instrumental tests, such as PET, CT and MRI. PET scan revealed abnormal extensive accumulations in the soft tissues of the left mammary region, the hepatic hilum lymph nodes, the liver and the lumbar spine. CT and MRI revealed right axillary adenopathy, uncertain supra and sub-diaphragmatic adenopathy and bone lesions in the right ilium.

In June 2012 the patient started the Di Bella Method.

Prescription included 0.5 g of Retinoic acid, 0.5 g of Palmitate axerophthol, 2 g of betacaroten, alpha tocopherol acetate 1,000 g, one dessert spoon three times daily at least 15 minutes before eating with Dihydrotachisterol 12 drops added to every spoon (36/day). Other medications included injections of Decapeptyl 3.75 mg i.m. every 4 weeks, Somatostatin 1 mg, Tetracosactide 0.25 mg, in the same syringe with somatostatin every other day, if compatible with blood pressure and glycemia. Slow-release octreotide 20 mg every 20 days and melatonin 5 mg, three tablets with the midday meal and with the evening meal and 10 tablets before going to bed (dissolved in water): 16 tablets a day, for a total of 80 mg, were added as well to the treatment.

The patient was also taking following medications: Dostinex half a tablet at midday twice a week, Parlodel 2.5 mg half a tablet twice daily, Arimidex once a day (replacing Tamoxifen), Endoxan 50 mg one tablet twice daily, Ascorbic Acid (Vit C) ½ teaspoon in a glass of water with the midday and evening meals with Calcium Sandoz ½ sachet in the same glass, Chondroitin sulfate 500 mg 2 tablets twice daily, Calcium levofolate 22 mg SD and Zofran in the event of vomiting.

The patient underwent biopsy of the bone lesions in the ilium which confirmed massive metastases of the breast carcinoma (ER 40%, PgR 10%, Her2 weak). A review of the slides with assessment of the chromogranin showed positivity in 20% of the tumor cells. After six months of DBM treatment PET scan showed more or less complete regression of the hepatic, bone and lymph node uptake.

In the control PET scan done in the January 2014, abnormal accumulations (except for aspecific splenic alterations) were not found. In January 2014 the patient also suspended the Endoxan-based therapy and continued with the hormonal/biological therapies. Subsequent instrumental tests showed complete remission of the disease. Since January 2014, the patient underwent several total body PET scans, last one in the May 2017, all of them with no recurrence of the disease.

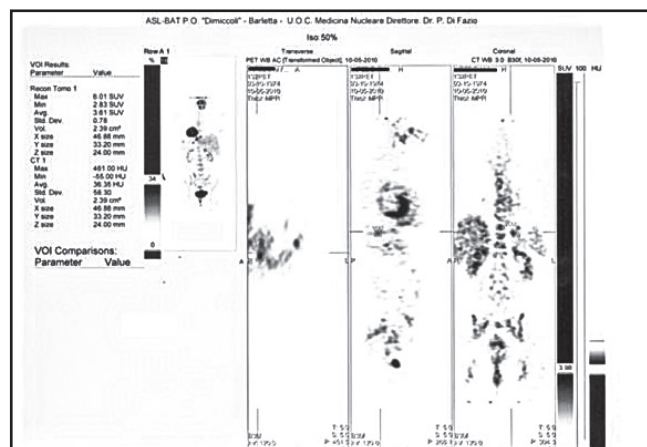


Fig. 1. THE CT scan showing multiple solid lesions of the spleen.

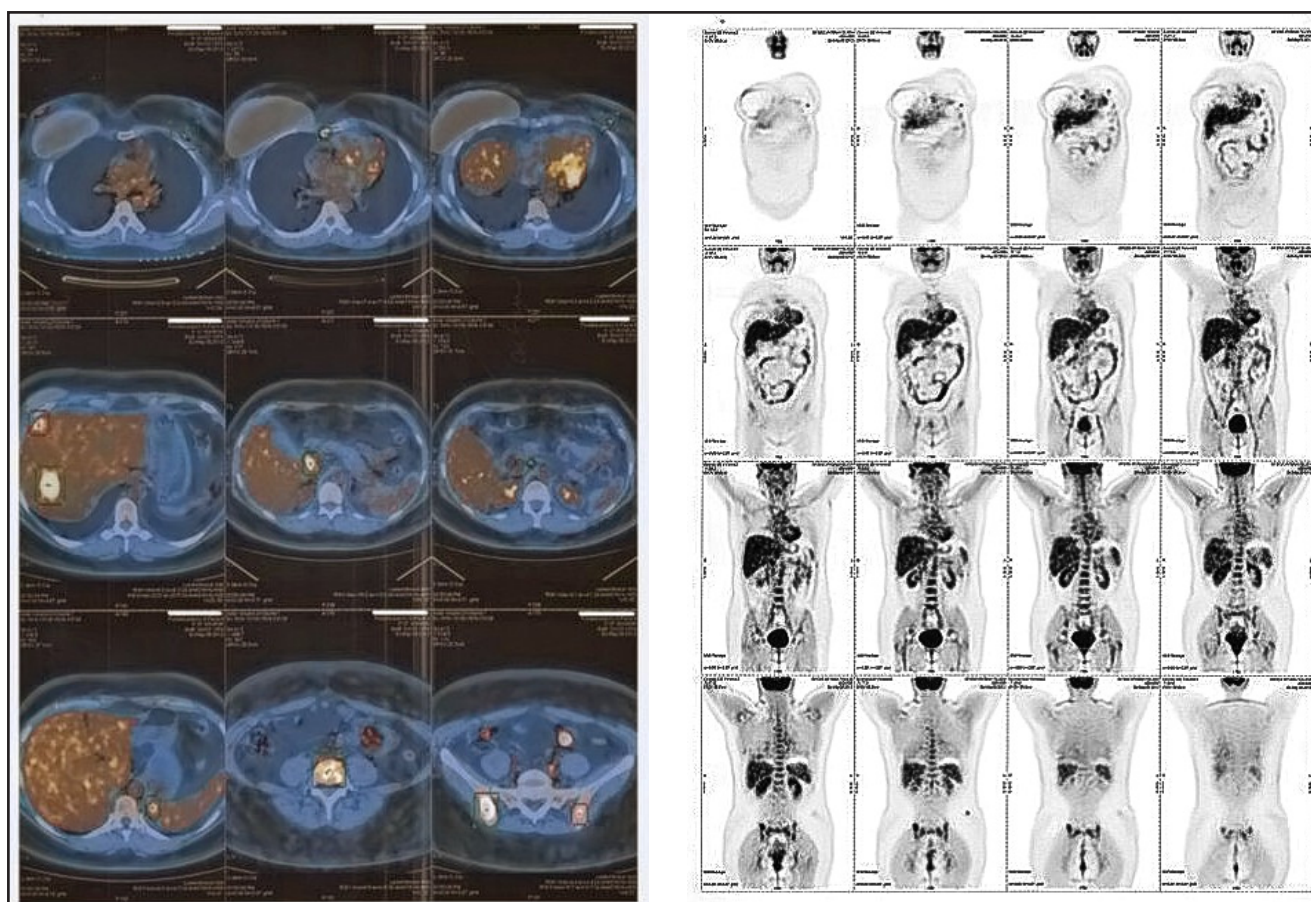
## THE THERAPY AND THE CLINICAL COURSE

In June 2012, due to recurrence of the disease and having refused a proposed second cycle of chemotherapy, the patient asked to be treated with the Di Bella Method, which consisted of the synergic use of molecules with differentiating, cytostatic, apoptotic, and antiproliferative activity, with an increase in immunitary activity. Due to the myeloprotective, antidegenerative and trophic action on the parenchyma and tissues, above all of MLT and the high doses of Vitamin E, retinoids, vitamins C and D3, the continuous administration for approx. 6 months of 100 milligrams of cyclophosphamide per day, together with all the components of the DBM, did not cause any medullary, hepatorenal, metabolic, cardiocirculatory or neurological toxicity or immunitary depression. It did not lead to any significant alteration in blood values and marrow dynamics. The Di Bella therapy includes Endoxan (cyclophosphamide) at doses varying from 50 to 100 mg a day for apoptotic purposes, not cytolytic as in oncological protocols. Comparing the 100 mg/day cyclophosphamide of the DBM with the intravenous 10 to 12 g in the pre-transplant therapies of lymphoproliferative diseases gives a ratio of 1 to 100. 100 mg, instead of 10 g, does

not have a cytolytic or cytotoxic effect, but apoptotic. In the time of six months, having the treatment at home, the patient achieved partial remission, afterwards complete remission, allowing her to return to work.

## DISCUSSION RATIONALE OF THE THERAPY

The loss of differentiation and proliferation, even if to different extents, are common denominators of all neoplasms. The ubiquitous receptor expression of prolactin (Ben-Jonathan *et al.* 2002; Hooghe *et al.* 1998) and GH (Lincoln *et al.* 1998; De Souza *et al.* 1974) are one of the confirmations of the direct and generalized mitogenic role of this molecule. Cellular proliferation is highly dependent on prolactin and GH, both powerful growth factors, and on GH dependent mitogenic molecules which are positively regulated by it, such as EGF, FGF, HGF, IGF1-2, NGF, PDGF, VEGF, and TGF in addition to growth factors produced by the gastrointestinal tract, such as VIP, CCK, and PG. Both physiological as well as neoplastic cellular proliferation take place by means of these same molecules, which the neoplastic cells use to an exponential extent compared to healthy ones. Biological antidotes of GH such as somatostatine and similar compounds, reduce not only the expression and



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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), but extend their negative regulation to the respective receptors with evident anti-proliferative and anti-angiogenic effects (Szepesházi *et al.* 1999, Mishima *et al.* 1999). The extent of the GH-IGF1 axis influence on neoplastic biological development is worth noting. The IGFs respond mitogenically to IGF. The suppressive effect of the SST and similar ones, on serum levels of IGF1, is both direct, by inhibiting the IGF1 gene, as well as indirect by suppressing GH and thus its hepatic induction of IGF1. Angiogenesis is essential to neoplastic progression. Angiogenesis is in turn regulated by the fall of monocytes, interleukin 8, and by growth factors such as VEGF, TGF, IGF1, FGF, HGF, and PDGF. Each of these factors is negatively regulated by somatostatin and similar drugs (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 synergistically enhanced by MLT (Lissoni *et al.* 2001; Di Bella *et al.* 1979; Di Bella & Gualano 2006), retinoids (McMillan *et al.* 1999; Kini *et al.* 2001; Majewski *et al.* 1994), vitamin D3 (Kisker *et al.* 2003; Mantell *et al.* 2000), vitamin E (Shklar & Schwartz 1996; Tang & Meydani 2001; Neuzil *et al.* 2002), vitamin

C (Ashino *et al.* 2003), prolactin inhibitors (Turner *et al.* 2000) and components of the extra-cellular matrix (Liu *et al.* 2005; Ozerdem & Stallcup 2004).

Likewise the cytostatic, anti-proliferative, and anti-metastatic effect of somatostatin is effectively synergized by MDB's other components:

- Retinoids (Hassan 1990; Voigt *et al.* 2000; Piedrafita & Pfahl 1997; Onogi *et al.* 1998)
- MLT (Bartsch *et al.* 1999; Kvetno & Levin 1986; Mediavilla *et al.* 1999; Maestroni *et al.* 1996; Cos *et al.* 2000)
- Vitamin D3 (Jensen *et al.* 2001; Barroga *et al.* 2000; Campbell *et al.* 2000)
- Cabergoline and bromocriptine (prolactin inhibitors) (Gruszka *et al.* 2001; Ben-Jonathan *et al.* 2002; Lissoni *et al.* 2001; Klijn *et al.* 1996; Manni *et al.* 1989)
- Glucosamine sulphate, galactosamine sulphate, components of the extra-cellular matrix (Pumphrey *et al.* 2002; Batra *et al.* 1997)
- Vitamin E (Turley *et al.* 1995; Israel *et al.* 2000; Malafa *et al.* 2002; Neuzil *et al.* 2002; Shklar & Schwartz 1996)
- Vitamin C (Head 1998; Murata *et al.* 1982; Cameron *et al.* 1979)

The causal relationship between GH's receptor expression and tumor induction and progression has been shown (Lincol 1998), histochemically demonstrating markedly higher concentrations of GHR in tumor tissues compared to physiological tissues, thus showing the powerful mitogenic role of GH with proliferative indices depending on dose. This is direct, via receptors, as well as indirect, by inducing hepatic expression of IGF1, which is GH dependent. The GH-IGF1 axis has a decisive role in the biological behavior of many neoplasms. In a very high percentage of neoplastic cells, IGF1 receptors have been identified which respond mitogenically to the ligand. Somatostatin exerts an antitumoral effect both directly, by inhibiting the IGF1 gene's expression, as well as indirectly, by suppressing GH, which is needed for IGF1 secretion (Pollak 1997; Schally *et al.* 2001; Schally & Nagy 2003). The SST inhibiting activity on EGF, another powerful mitogenic growth factor, with multiple mechanisms, has also been thoroughly documented:

- depending on the dosage, inhibition of tyrosine phosphorylation induced by the activation of EGFR by EGF (Mishima *et al.* 1999);
- reduction of EGFR in tumor cells (Szepesházi *et al.* 1999);
- reduction of EGF's expression (Held-Feindt *et al.* 1999);
- reduction of EGF's plasma concentration (Cascinu *et al.* 2001).

Mitogens produced by the gastrointestinal tract such as VIP, CCK, and PG are strongly inhibited by somatostatin and/or octreotide (Kath & Höffken 2000). It has

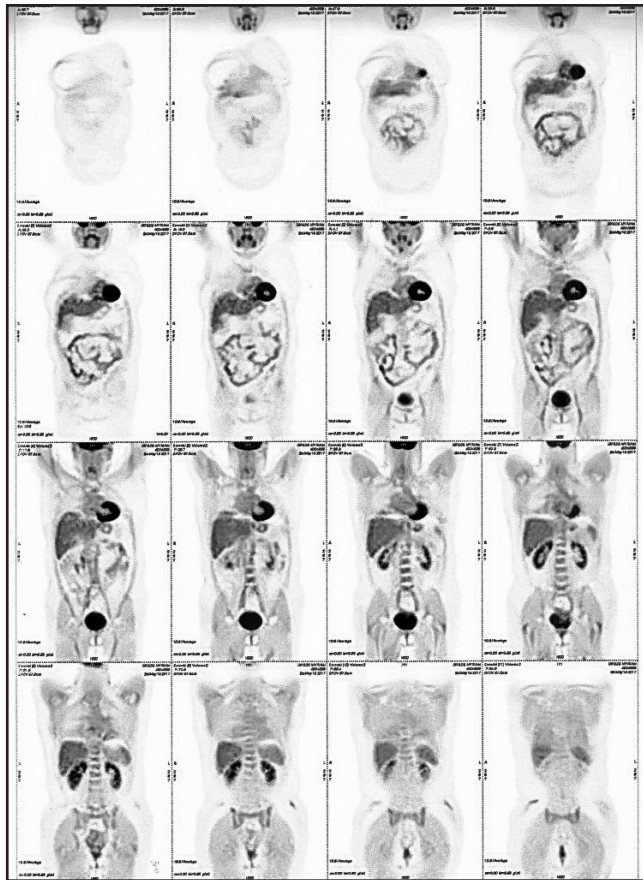


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been shown that breast tumors express SSTR1, SSTR2, and SSTR3, and less frequently SSTR5 (Albérini *et al.* 2000; Schaer *et al.* 1997),

Complete objective response to biological therapy of plurifocal breast carcinoma which in at least 50% of cases is scintigraphically visible, while in over half of the negative scintigraphs histochemical examinations revealed the presence of SSTR. Therefore the presence of SSTR (Barnett 2003; Pinzani *et al.* 2001; van Eijck *et al.* 1998), and of neuro-endocrine receptors in a significant percentage of these carcinomas constitutes a further rational indication for using SST, which in any case has already been extensively justified by the above-cited negative effect of SST on GH, GH-correlated oncogenes and angiogenesis.

Angiogenesis and neoangiogenesis, necessary conditions for tumour progression, as well as the cascade of monocytes, the paracrine release of interleukin 8 (IL-8) and the contribution of GFs (whose synergism is essential), are specific molecular targets negatively regulated by Somatostatin and its analogues (Ruscica *et al.* 2012). The inhibition of angiogenesis induced by SST is synergistically reinforced by MLT, Retinoids and vitamin D3 (Kim *et al.* 2013; Lissoni *et al.* 2001; Sogno *et al.* 2009; Picotto *et al.* 2012). Furthermore, the local conditions of hypoxia/ anoxia and acidosis promote angiogenesis, and are mostly corrected by the improvement in the bloodtissue exchanges induced by the differentiating components of the DBM. At the same time, the cytostatic, antiproliferative, and antimetastatic effects of Somatostatin are synergistically increased by the other components of the DBM. An additional contribution is provided by the daily administration of low doses (50–100 mg/die per os) of Cyclophosphamide (Endoxan®). As well as drastically reducing the known anitblastic/myelosuppressive effects, this dosage induces a marked turnaround of its mechanisms of action: triggering of the mitochondrial-dependent apoptotic cascade, anti-angiogenetic action by drastically down-regulating the VEGF gene expression (Loven *et al.* 2013). Numerous preclinical investigations have also demonstrated the mechanisms of action of MLT. The use of such indole extends to all histotypes of breast cancer due to its high membrane receptorial/ nuclear distribution (Oprea-Illies *et al.* 2012; Röglersperger *et al.* 2011). Since the molecule is associated with the signalling pathways of both the physiological and neoplastic epithelial development, this substance has the properties to selectively neutralize the proliferative signals of estrogens and negatively modulate their local biosynthesis (Hill *et al.* 2011; Girgert *et al.* 2009). The administration of low doses of second generation aromatase inhibitors (Anastrozole®), already used in clinical practice, combined with MLT, SST and Retinoids, negatively regulates the hormone-dependent processes of proliferation of breast tumours (Alvarez-Garcia *et al.* 2013; Margheri *et al.* 2012; Wang *et al.* 2012; Knower *et al.* 2012; Ciolino *et al.* 2011).

The biological DBM therapy slowly and progressively achieved a complete objective response, without toxicity, through a receptorial, differentiating, apoptotic and antiproliferative mechanism of action, with criteria, aims and mechanisms of action totally differing from the usual cytotoxic and cytolytic therapies.

The objective response to the DBM (Di Bella Method) extended to resolution of the hepatic, lesions, thoracic lymphadenopathies, axillary adenopathies, supra- and sub-diaphragmatic adenopathies, and bone and splenic lesions which were no longer detected. Thanks to the progressive reduction, and complete elimination, of the metastatic lesions, the objective non-toxic result shows the efficacy and tolerability of this treatment.

**Competing Interest.** All the authors declare that they have no competing interest.

**Autor's Contribution.** GDB were responsible for conception and interpretation for the provision of study material and manuscript writing. RT and BC responsible for conception. All authors read and approved the final manuscript

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