The Di Bella Method (DBM) in the treatment of prostate cancer: a preliminary retrospective study of 16 patients and a review of the literature

Giuseppe Di Bella [1], Fabrizio Mascia [1], Biagio Colori [2]

1 Di Bella Foundation, Via Guglielmo Marconi, 51 40122 Bologna, Italy
2 Rizzoli Scientific Research and Care Institute, Via Giulio Cesare Pupill, 40136 Bologna, Italy

Correspondence to: Dr. Giuseppe Di Bella
Di Bella Foundation, Via Marconi 51, Post code 40122, Bologna, Italy.
TEL: +39 051 239662; FAX: +39 051 2961238; E-MAIL: posta@giuseppedibella.it

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Abstract

OBJECTIVE: To evaluate the objective clinical response and the safety of the combined administration of somatostatin, melatonin, retinoids, vitamin D3, dopamine subtype 2 receptor (D2R) agonists and low doses of cyclophosphamide, associated with androgen ablation, in patients with a histological diagnosis of prostate adenocarcinoma (Pac).

MATERIALS AND METHODS: The clinical data of 30 patients with non-invasive and metastatic prostate cancer, who attended our institution over a period of more than 5 years, were retrospectively reviewed.

RESULTS: 16 patients satisfied the evaluation criteria. Median age: 64 years. Disease stages: 8 patients (50%) were in Stage II. For advanced stages (Stage IV), secondary lesions were located in the bones and lymph nodes. Taken together, an overall objective response (OR) [Complete response (CR) + Partial Response (PR)] was achieved in 69% of the patients, with 88% of objective clinical benefit [CR+PR+SD]. For local Prostate Cancer group, an OR was achieved in 87.5% of patients (7 cases; 53–98; 95% CI), with CR in 62.5% (5 cases, 31–86; 95% CI). In metastatic disease, the OR was 50% (4 cases; 21–78; 95% CI), with a 20% of CR (2 cases; 7–59; 95% CI) and 75% of clinical benefit.

CONCLUSIONS: This preliminary study shows that patients with early and advanced forms of prostate cancer, not previously treated by surgery and/or chemo-radiotherapy, can achieve a more than positive clinical benefit with the protocol foreseen by the Di Bella Method. Further clinical investigations are strongly recommended.

ORIGINAL ARTICLE

INTRODUCTION

The main therapeutic strategies currently employed for the treatment of Pac are surgery (*laparoscopy and/or prostatectomy*), chemotherapy and radiation therapy (*external beam radiation and/or LDR and HDR brachytherapy, IMRT*), often associated with hormone therapy (LH-RH agonists, anti-androgens). Although these treatments have achieved modest results in terms of survival, the anticancer efficacy is usually limited to remission while cases of actual stable cure are considerably limited. This is mainly due either to the tumor clonal heterogeneity, which makes them less responsive to such treatments, and to the complexity of their cellular pathways; even after several

new molecules were provided during the last decade (Bostwick *et al.* 2005). In fact, the removal of just one causal factor (like androgen)/ single target by using the latest generation of monoclonal antibodies obviously cannot eradicate a complex multifactor disease like cancer. A series of concepts forming the basis of the Di Bella (DBM) have recently been assessed and applied, including the combined use of "multiple molecular target" agents; and experimental investigations confirming the biochemical basis and the clinical responses of these therapeutic concepts are continually increasing in number (Sluka *et al.* 2013; Koutsilieris *et al.* 2006). Especially as regards basic research, these investigations are clearly demonstrating the crucial oncogenic, ubiquitary and interactive role of growth hormone (GH) and Prolactin (PRL) in every type of tumor. These pituitary hormones thus also strongly affect both the development and differentiation of Pac. Finally, translational and clinical studies confirm the use of the respective neoplastic growth inhibitors, reporting considerable benefits in terms of clinical response and safety/tolerability (Xu *et al.* 2012; Letsch *et al.* 2004; Schally *et al.* 2000). In the present study, we report the preliminary results achieved from the administration of biological molecules (Di Bella Method, DBM) in 30 patients affected by local and metastatic prostate cancer.

MATERIALS AND METHODS

Patient selection criteria

Only patients with a diagnosis of prostate cancer and with the measurable disease characteristics according to RECIST (Vergote *et al.* 2000) were evaluated. All patients gave informed consent, agreeing to the administration of the biological approach as first line therapy.

This patient collection was divided into two main groups:

- Group A: patients with local/non-invasive prostate cancer (Stage II: pT_2, N_0, M_0)
- Group B: patients with metastatic prostate cancer (Stage IV: any pT, any N, M_1)

Treatment

All patients received a daily dose of Somatostatin (SST), Melatonin (ML), Retinoids solubilized in Alfa Tocopheryl Acetate, D_2R dopamine agonists, androgen inhibitors and minimal doses of cyclophosphamide. In detail, these were administered as follows: solution of all-trans-retinoic acid (ATRA, 1 453 488.372 IU), axeroftole palmitate (909 000 IU), beta-carotene (3 334 000 IU) in alfa tocopheryl acetate (1 000 000 IU), at the stochiometric ratio of 1:1:4:2; gradual dosage; together with dihydrotachysterol (cholecalciferol-Vit.D_3, ATITEN©; 15 200 IU). Somatostatin tapered administration: 1 mg the first week, increasing by 1 mg a week up to 3 mg at treatment day 21; Tetracosactide (Synachten® – synthetic ACTH) with frequent blood pressure and blood sugar monitoring: 0.25 mg twice a week intramuscularly; slow-release octreotide 20 mg every month intramuscularly; melatonin 5 mg *per os:* 10 mg in the morning, at midday, and in the evening at mealtimes plus 40 mg before bedtime (overall daily dose = 70 mg); Cabergoline (Parlodel®) 0.25 mg *per os* at midday (half a 0.5 mg tablet) twice a week along with Bromocriptine (Dostinex®) 2.5 mg *per os* 1 tablet morning and evening; Cyclophosphamide (ENDOXAN® 50 mg) *per os,* gradual dosage: starting with 1 tablet a day, after one week 1 tablet in the morning and 1 in the evening; Ascorbic Acid (Vit C) *per os*, gradual dosage (2 g = 40 000 IU) in a glass of water at midday and in the evening during meals, with 500 mg of calcium in the same glass; Taurine (500 mg) one tablet in the morning and in the evening; Chondroitin sulphate (500 mg) one tablet in the morning, at midday and in the evening during meals; Intrafer® 20 drops with the main meal; Calcium levofolinate 22 mg one tablet a day. More details regarding methods of administration, concentrations and respective doses are provided in Table 5.

Evaluation of the response to treatment of the target lesions (Efficacy)

Statistical and Analytical Methods: the criteria for evaluation of the objective response refer to the guidelines adopted by the World Health Organization (*WHO handbook*) and the *Response Evaluation Criteria in Solid Tumors* (Patrick *et al.* 2000). These are divided into Overall Response (OR); Complete Response (CR); Partial Response (PR); Progressive Disease (PD); Stable Disease (SD), expressed as absolute frequency (n), relative frequency (%) plus 95% Confidence Interval (95% CI).

Safety and Toxicity Evaluation

To evaluate toxicity, only the adverse events that could potentially be correlated with the treatment were considered (degrees of correlation*: possible, probable or certain,* expressed as absolute frequency (n), relative frequency (%), and 95% Confidence Interval (95% CI).

This study was carried out in accordance with the directives established by the *Declaration of Helsinki*. All patients therefore gave their informed consent for the collection and supervision of their own clinical data.

RESULTS

The biological therapy

DBM was administered as first line treatment to a total of 30 patients who attended our institution over a period of more than 5 years. The patients were monitored from 2009 to 2012 (median *follow-up* 16 months, min 5, max 37). Sixteen (16) of these patients fulfilled the inclusion criteria and their clinical records were therefore retrospectively assessed. As regards the excluded cases (14), 8 did not have any hystological diagnosis while 6 patients did not followed the regimen continuously (see flow-chart). Table 1 shows the baseline charac-

Tab. 1. Summary of Clinical Data at baseline visit.

		Abs. Freq.	Rel. Freq (%)
Median Age (Min – Max)		64 (40–74)	– –
ECOG (PS)	Grade 1	2	12.5
	Grade 2	8	50
	Grade 3	6	37.5
Histotype		Adenocarcinoma	
Histologic Grade (*Gleason Score*)	G6	6	37.5
	G7	10	62.5
Site of the Metastases	Bone	12	80
	Lymph-nodes	4	20

Tab. 2. Global effectiveness with DBM in Prostate Cancer (Groups A+B).

Resp. Rate	Cases Abs.Fr	Rel. Fr. (%)	95% CI
CR	7	44	18; 62
PR	4	25	10; 49.5
SD	3	19	6.5; 43
P	2*	12	3.5; 56

Response Rates (N=16). CR: Complete remission; SD: Stable disease, PR: Progression. * Dead patients

Tab. 3. Group A (Local/non-invasive prostate adenocarcinoma, N_A= 8). Overall objective responses.

Resp. Rate	Cases Abs.Fr	Rel. Fr. (%)	95% CI
CR	5	62.5	21; 79
PR	2	25	7; 59
SD	1	12.5	2.24; 4.7
P	0	–	–

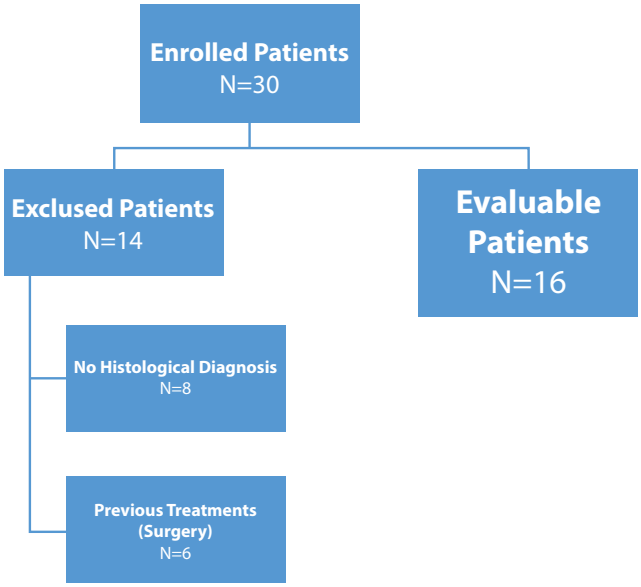
CR: Complete remission; SD: Stable disease, PR: Progression. * Dead patients

Tab. 4. Group B (Metastatic prostate adenocarcinoma, N_B= 8). Overall objective responses.

Resp. Rate	Cases Abs.Fr	Rel. Fr. (%)	95% CI
CR	2	25	7; 59
PR	2	25	7; 59
SD	2	25	7; 59
P	2*	25	7; 59

CR: Complete remission; SD: Stable disease, PR: Progression. * Dead patients

teristics of the patients at the time of their first visit: median age 64 years (range 40–74 years), disease stage = grade 6 and 7 (Gleason Score) in 37.5% and 62.5% of



Flow-chart. Patient enrolment criteria.

the patients respectively. The histotype of the primary lesions was *Prostate adenocarcinoma* (Pca), while bones and lymph nodes represented the main metastatic sites. Taken together, an overall response (OR) [Complete response (CR) + Partial response (PR)] was observed in 69% of the patients (11 Cases, 44–86 95% CI), with a Complete Response equal to 44% (7 cases; 23–67; 95% CI). In addition, 87.5% (14 cases; 57–93; 95% CI) of the patients achieved an objective clinical benefit [CR+PR+SD] (Table 3). *Group A (Local/Non Invasive Prostate Cancer,* Stage II, pT_2, N_A*=8):* an OR (CR+PR) was observed in 87.5% of the patients (7 cases; 41–93; 95% CI), with a CR in 83% of the cases (n=5, 22–79; 95% CI). The mean time to the first objective clinical response was 6 months: furthermore, all the patients obtained a clinical benefit [CR+PR+SD]. For patients with metastatic disease *(Group B, Metastatic,* Stage IV, pT_2*, any N,* M_1*,* N_B*=8)*, the OR (CR+PR) was 50% (4 cases; 22–79; 95% CI), with a CR in 25% of the cases (2 patients; 7–59; 95% CI). Six cases (75%) achieved a clinical benefit [CR+PR+SD].

Evaluation of the safety

The most frequent transitory signs of toxicity (grade II) were as follows: haematological (mild leukopenia 61.5%), gastrointestinal (Nausea, 30%), and tiredness (8%). Reduction, suspension or discontinuation of the treatment due to toxicity was necessary in patients with leukopenia (suspension of cyclophosphamide until normal blood count values were restored), and in cases of gastrointestinal symptoms.

DISCUSSION

Rationale of the treatment and review of the literature

A greater understanding of the biological and physiological basis of cancer ethiopathology has gradually

led to the identification of new molecular cues involved in these complex cellular pathways and to propose new evermore specific strategies for the treatment of hormone-dependent tumors (e.g. breast cancer and Pca). It is well known that cellular growth mechanisms of prostate cancer are mainly based on the androgenic action and on the concomitant neuroendocrine action, with special reference to the role of other growth factors (GFs) released both by the hypothalamic-pituitary axis (*Growth Hormone Release Hormone*, GHRH; GH and PRL) and systemically (Takanara *et al.* 2013; Nakonechnaya *et al.* 2013; Goffin *et al.* 2011). Agonists and antagonists molecules of the luteinizing hormone release hormone (LHRH), antagonists of gastrin and mammal bombesin homologues, growth hormone release hormones (GHRH), somatostatin analogues and dopaminergic agonists were in fact evaluated (Xu *et al.* 2012; Schally *et al.* 2000). Although their use in clinical practice has been limited to neuroendocrine tumors (NET), there is increasing significantly important evidence in the literature both of their gene expression and receptorial immunohistochemical localization/co-localization in several non-NET: similar data were also obtained for *Vasoactive Intestinal Peptide* (VIP) and somatostatin (SSTR), whose expression has been detected both in various forms Pca, in its precursor (HGPIN) and normal epithelium (Nep) (Mazzucchelli *et al.* 2012). Similarly, significant results have been observed for all types of non-NET, providing further evidence of the rationale of the DBM with somatostatin analogues combined with cytostatic and differentiating molecules used as a "receptorial target biological therapy" against the tumor phenotype (Di Bella 2010). This strategy extends its action to the different stations of the hypothalamic-pituitary-hepatic axis and is not limited to the simple direct activation of the antiproliferative pathway (Msaouel *et al.* 2009). In fact, the other fundamental, indirect anticancer

Tab. 5. DBM Therapeutical Regimen. * These molecules are mixed in solution form, a formulation which allows maximum bioavailability. The daily dose is calculated on the basis of body weight decimals; **** Can be used together with or instead of Bromocriptine.

Drug	Chemical Information	Dosage	Route of administration	Frequency
Somatostatin	14 aa peptide	3 mg	subcutaneous	Daily (nightly, 12 hours of infusion)
Octreotide (LAR)	Octreotide Acetate 8 aa	20 mg	intramuscular	Every 20 days
Melatonin	Melatonin 12 % Adenosine 51 % Glycine 37 %	70-100 mg	*per os*	Daily
Retinoid Mixture *	All-Trans-Retinoic acid	0.5 g (46 662 IU*)	*per os*	Daily (3 times)
	Axeroftole-Palmitate	0.5 g (25 452 IU*)		
	Beta-Carotene	2 g (93 352 IU*)		
	Alfa Tocopheryl Acetate	1 000 g (38.08 IU*)		
Vitamin C	L-Ascorbic Acid	2-4 g (40-80 × 10^3 IU)	*per os*	daily
Vitamin D_3	1.25-diOH-Tachysterol	(15 200 IU)	*per os*	Daily (3 times)
ACTH	Tetracosactide Acetate	1 mg	intramuscular	Once a week
PARLODEL	Bromocriptine	2.5 mg ****	*per os*	Daily
DOSTINEX	Cabergoline	0.5 mg		Twice a week
Endoxan	Cyclophosphamide	50 mg	*per os*	Daily
Calcium	Calcium lactate gluconate + Calcium carbonate	2 g	*per os*	Daily
Androgen	Leuprorelin	3.75 mg	parenteral	Monthly
Inhibitors	Triptorelin		parenteral	Monthly

mechanism is achieved by reducing the bioavailability of GH, hepatic somatomedines (IGF-I) and all the GH-dependent GFs, released in the tumor microenvironment responsible for tumor progression phenomena, such as cancer cell motility, methastasis and clonal heterogenecity (Russel *et al.* 1998). Reduced GH bioavailability therefore inhibits neoplastic angiogenesis, negatively regulating the growth factor's releasing, and so the angiogenesis-promoting molecules of the systemic microenvironment of the tumor with a strong/significant antiblastic efficacy (Friedlander *et al.* 2009; Erten *et al.* 2009). It has also been observed that this biological approaches restores the responsiveness of tissues towards antiandrogens, thereby obtaining objective clinical responses. At the same time, the crucial role of the D_2R receptors has been confirmed, both in the direct control of cell growth and in the antiproliferative interaction with somatostatin: their proliferation pathway is in fact significantly inhibited when this particular subclass of receptors synergically cross-talk in association with the SST5 receptorial subclass ($SSTR_5$) (Arvigo *et al.* 2010). This type of androgen deprivation allows an up-regulation of the SSTR receptors, thus increasing the probability of a positive response (Mazzucchelli *et al.* 2011). It has also be shown that tochopherole, another component belonging to the DBM, increases such receptorial expression of somatostatin, with evident increase of the antiproliferative effects. The cytostatic-antiproliferative properties of SST in prostate cancer are mediated in their pathway by the citosolic phosphotyrosine phosphatase (SHP-1). Finally, these data suggest a dynamic receptorial interaction induced by the ligands SST and Bromocripine/Cabergoline, whose interplay might be fundamental for a marked anticancer action (Zapata *et al.* 2004). This increase in antiproliferative responsiveness is further obtained by the primary contribute of Melatonin (ML), retinoids and Vitamin D_3, whose antitumoral properties are well known: ML exerts many antiproliferative properties by promoting cell differentiation towards the neuroendocrine phenotype (epigenetic-control), the latter being characterised by androgen-dependent type growth (Shiu *et al.* 2010). The cell differentiation promoted by ML is not exclusively mediated by the protein kinase A (PKA) activation (although this temporarily increases the intracellular levels of cyclic adenosine monophosphate, cAMP).ML also markedly affects the proliferative condition of the prostate cancer cells by acting through their membrane and nuclear cellular/nuclear receptorial pathways. Together with the above data, our results indicate the antiproliferative synergism between melatonin and androgen deprivation in androgen-sensitive tumors. This dual action of such antiproliferative signal suggests a specific mediation of the MT1 receptorial pathway towards the down-regulation of the AR-dependent signal and and an up-regulation of the p27 gene expression. The phenotype changes caused by the chronic treatment of this indolamine thus make the cells more responsive to the action of cytokines (TNF-alfa and TRAIL), SST, androgenic antagonists and some chemotherapy components, if administered at low doses (metronomic chemotherapy). (Rodriguez-Garcia *et al.* 2012; Chun *et al.* 2009; Park *et al.* 2009, Siu *et al.* 2002; Limonta *et al.* 1995). Another important contribute is provided by cholecalciferol, acting through its nuclear receptor VDR (Leyssens *et al.* 2013). Actually, It has be well known that this type of lyposoluble prohormone exerts several oncosuppressive activities, also by interacting with the other components of the multitherapy in inhibiting cancer cell proliferation and in triggering the apoptosis cascade, differentiation, reduction of cell invasion, angiogenesis, and migration/invasion (extracellular inhibition/gene downregulation of Matrix Metalloproteinases MMP and the expression of the cell membrane adhesion molecules and promotion of cell adhesion through an increase in the expression of E-caderine, regulation of the chemotaxis of adhesion cells towards the blood circulation, with an antimetastatic effect) both *in vitro* and *in vivo* (Yin *et al.* 2009). In addition, the synthesis of the prostaglandins and the Wnt/b-catenine signal are also influenced by vitamin D_3 and analogues (Okamoto *et al.* 2012; Stio *et al.* 2011; Hsu *et al.* 2011). Finally, retinoid are a family of organic compounds that are used for the treatment of various diseases, also including many forms of tumors of the blood. This class of molecules are fundamental for the normal development of the prostate and negatively regulate the growth of various prostate cancer cell lines and their progression in *vivo*. Among the retinoid, all-trans-retinoic acid (ATRA) has been widely studied, showing a marked differentiating activity. One of the mechanisms of action consists of the reduction of methylation processes (epigenetic modulation) at the level of the HOX genes (HOXB3) and the regulation of the formation of gap junctions in androgen-responsive prostate cancer cells (Liu *et al.* 2012; Kelsey *et al.* 2012). Overall, numerous *in vivo* and *in vitro* studies have shown that ATRA slows down tumor cell proliferation, inducing apoptosis (surviving down-regulation). One of the anticancer mechanisms is represented by the selective regulation (p21 and p27) with which ATRA is able to inhibit the typical proliferative processes of prostate cancer. Since the retinoid act by inducing cell differentiation and maturation, it is clear that they are probably of use in reversing neoplastic pathogenesis (Benelli *et al.* 2010). Other recent molecular targets include retinoid receptors (RAR and RXR), glucocorticoid receptors (GR), oestrogen receptors (ER) and the receptors activated by peroxisomes (PPAR).

CONCLUSIONS

Although our preliminary results are based on a relatively small number of subjects, they suggest that patients affected by local and/or metastatic prostate cancer, can achieve encouraging results with the com-

bination of the above mentioned biological approach. A further support is given by the several pre-clinical and clinical investigation that are gradually suggesting the potential antitumoral role of the biological compound belonging to the DBM. Since the results regarding surgical – radiotherapy standard treatments are contradictory and because it has been recently shown that chemotherapy improves prostate cancer resistance and progression (Sun *et al.* 2012), we suggest further clinical studies in order to investigate the first line use of this multimodal treatment and its putative application in medical oncology.

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