The Di Bella Method (DBM) improved survival, objective response and performance status in a retrospective observational clinical study on 55 cases of Lymphomas

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Abstract

OBJECTIVES: Lymphomas are the main form of haematological neoplasms, representing 55.6% of all tumours of the blood. Overall, they account for 5.3% of all malignant tumours (excluding basal and squamous cell skin cancer) in Italy with a prevalence constantly increasing at a rate of 3% per year. From a histological point of view, they represent a vast heterogeneous group of haematological diseases, their staging being based on defined cyto-morphological and anatomo-pathological criteria. Although the combined use of standard approaches can provide good response rates, recurrence is particularly frequent in patients undergoing traditional treatment, with critical and often irreversible side effects such as myelosuppression and a high frequency of opportunistic infections and sterility. Numerous epidemiological studies and preclinical data have for some time now reported the anticancer effects of molecules such as Melatonin, Retinoids, Vitamins E, D3, and C, Somatostatin and prolactin inhibitors in neoplastic diseases. There are, however, very few publications on the combined effects of these substances *in vivo.*

METHODS: We report an observational study carried out on 55 patients affected by various forms of lymphoma, treated with the biological therapy known as the Di Bella Method (DBM). The 1, 3 and 5-year survival rates are reported, together with any signs of toxicity.

RESULTS: The DBM treatment achieved partial or complete objective responses in a shorter time and in greater percentages if administered as first-line therapy. The adjuvant treatment increased survival time and improved quality of life with respect to the data reported in the literature for the same types and stages of lymphoma.

CONCLUSION: Overall, the treatment was well tolerated, with minor and transient side effects. The patients were able to continue the treatment at home, carrying out their normal activities without problems.

ORIGINAL ARTICLE

INTRODUCTION

Malignant lymphomas represent the fifth most frequent type of tumour in the western world, with an incidence of around 20 cases per 100,000 inhabitants. The relative survival of patients with Hodgkin's lymphoma (HL) is, respectively, 93% at 1 year, 87% at 3 years, and 84% at 5 years (Morton *et al.* 2006).

As far as non-Hodgkin's lymphomas (NHL) are concerned, the respective percentages are 80% at 1 year, 73% at 3 years and 71% at 5 years, with slight variations depending on the sub-type (Italian Tumour Registry). In Italy, estimates indicate 70,130 new cases in 2012 alone, with 18,940 deaths (Luminari *et al.* 2007). Various types of treatment are currently available for lymphomas, their objective essentially being remission for as long as possible. Some treatments are defined as standard and foresee the use of alkylating agents (poly-chemotherapy), corticosteroids, and purine analogues, while others are still in the clinical study phase (e.g. monoclonal antibodies). Although the combination of these molecules can even lead to a long-term response, recurrence, severe toxicity, such as myelosuppression, and risk of infection are frequent, with the inevitable involvement of stem cells following autologous transplants and the subsequent use of antibiotic, antiviral and antimycotic treatments. These conditions are extremely invalidating, with a negative effect on quality of life and percentage of remission (Danilenko & Shakhmarina 2012; Gafter-Gvili *et al.* 2012; Schmitz *et al.* 2012; Zyrina, 2012; Farha *et al.* 2011; Atra *et al.* 1998).

The aim of this study was to investigate the efficacy and safety of the DBM through the combination of Somatostatin, Bromocriptine, Retinoids, Melatonin, ACTH and low doses of cyclophosphamine on 55 patients affected by lymphoma.

Tab. 1. Patient characteristics.

	Cases	%
Gender		
Male	32	58
Female	23	42
Previous treatments		
Surgery (group)	4	11
Chemotherapy (group)	12	33
Surgery + chemotherapy (group)	16	44
Chemotherapy + radiotherapy (group)	2	5
Radio (group)	2	5
ECOG PS		
0	8	15
1	12	22
2	14	25
3	13	23
4	8	15
Age		
Median	56	
Range	Min 16 - Max 92	

PATIENT ENROLMENT AND METHODS OF ANALYSIS

A total of 55 patients affected by lymphoproliferative disorders were enrolled in the study. Thirty-six (47%) of these presented recurrent and/or refractive forms of lymphoma. Thirty-two patients (58%) were male and twenty-three female (42%). The mean age of the patients was 57 years (min 19; max 95). Twelve patients (22%) were affected by Hodgkin's lymphoma and 43 (78%) by non-Hodgkin's lymphoma (Table 1). Staging at the time of enrolment was as follows: stage I – 13 cases (24%), stage II – 15 cases (27%), stage III – 10 cases (18%), stage IV – 17 cases (31%) (Figure 1).

The most representative forms of the NHL cases were the follicular subtype (13 cases = 30%), while 15 cases (35%) were diffuse large B cell lymphoma (DLBCL) and 5 cases (12%) of Burkitt lymphoma. The patients with Hodgkin's lymphomas included 8 cases (25%) of the classic scleronodular form. Localization of the lesions was as follows: upper extremities (15.53%), lower extremities (8.62%), head and neck (17.24%), thoracic (17.24%), retroperitoneal (6.8 %), uterine (3.44%), abdominal (20.7%) and pelvic region (10.34%).

The main inclusion criteria were a histological or cytological diagnosis of neoplastic disease, the presence of measurable and/or assessable disease, having stopped antiblastic treatment at least four weeks before starting the DBM treatment and not having previously received DBM treatment.

In addition, the following exclusion criteria were applied: patients who did not provide informed written consent; patients who did not have histo-cytological confirmation of a specific neoplastic disease; patients who had started the experimental treatment before enrolment; patients who underwent the basal evaluation after starting the treatment; patients who did not start the experimental treatment after enrolment.

These exclusion categories were monitored for the sole purpose of evaluating the toxicity of the treatment.

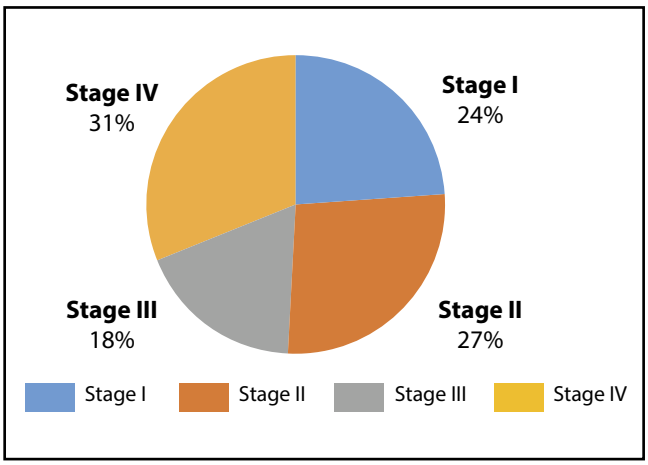

Fig. 1. Patient enrolment. Lymphoma staging.

Patients in progression or who died before the final evaluation were, however, included.

The patients considered eligible for enrolment were divided into the following groups:

Group A (19 cases, 35%**):** patients given the DBM treatment as first-line therapy;

Group B (36 cases, 65%**):** patients in progression who started the DBM after surgery, chemo and/or radiotherapy (previous treatments + DBM).

Group B patients were divided into the following subgroups: *B1*: 12 cases (33%), **chemotherapy only**; *B2*: 4 cases (11%), **surgery only**; *B3:* 2cases (5%), **chemotherapy + radiotherapy**, *B4:* 16 cases (44%) **surgery + chemotherapy**; B5: 2 cases (5%) **radiotherapy only**.

Data collection

For each patient enrolled in the study, a specific form containing clinical information was prepared. These forms included the following sections:

First section: basal evaluation at the time of patient enrolment. This section indicates the stage of the disease, the sites of the lesions (staging) the haematological parameters and the specific tumour makers;

Second section: periodic evaluation; regarding re-assessment of the sites of the lesions and the haematological parameters (re-staging), together with information on any undesired side effects of the treatment;

Third section: clinical conditions of the patient up to the end of the study (follow-up).

Therapy protocol

All the patients received a daily combination of somatostatin plus retinoids, melatonin, vitamin C, Vit. D, Bromocriptine and low doses of Cyclophosphamide. The respective doses and methods of administration are indicated below (Table 2).

Evaluation of the anticancer activity

This parameter is expressed in proportion to the partial and complete objective responses, defined according to the World Health Organisation (WHO) guidelines (Therasse *et al.* 1999). Clinical evaluation was carried out during the re-staging periods of the disease.

On the basis of the criteria adopted for response evaluation in the event of a complete and/or partial response, definitive confirmation after 4 months of DBM treatment was necessary.

To assess the anticancer activity of the treatment, all patients were classified during the re-assessment period on the basis of the following outcomes: complete/partial response after 4 months, progression of the disease, stability, death, voluntary suspension, discontinuation due to possible toxicity.

A follow-up study was carried out for survival analysis. Overall survival (OS) and 1, 3 and 5-year survival were used to evaluate the clinical data.

A survival curve (*intent-to-treat*, ITT) was also plotted from the time of enrolment up to the end of the study (60 months). Progression-free survival (PFS) and Overall survival (OS) were then calculated from this curve.

Tab. 2. The Di Bella Method (DBM).

Drug	Chemical Information		Dose	Route of administration	Frequency (Time)
Somatostatin	14 aa		3 mg	subcutaneous	Daily (at night, 12 hours)
Octreotide	Octreotide Acetate 8 aa		1 mg	subcutaneous	Every 28 days
Melatonin	Melatonin Adenosine Glycine	12 % 51 % 37%	20–60 mg	per os	Daily
Retinoids	All-Trans-Retinoic acid Beta-Caroten Axeroftol-Palmitate In Alfa Tocopheryl Acetate	0.5 g 0.5 g 2 g 1000 g	 **	per os	Daily (3 times)
Vitamin C	Ascorbic Acid		2–4 g	per os	Daily
Vitamin D	1,25-diOH-Tachysterol		***	per os	Daily (3 times)
Bromocriptine Cabergoline			2.5 mg**** 0.5 mg	per os	Daily Twice a week
Cyclophosphamide Calcium			50mg 2 g	per os per os	Daily Daily

** 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; an adult weighing 70 kg can thus take 7 g of solution 3 times a day.

*** synthesized Vit D_3, 10 drops before meals together with the solution

**** Can be used together with or instead of Bromocriptine

Toxicity assessment

All undesired effects were evaluated according to the degree of correlation with the treatment, in accordance with standard criteria (plausibility of the time interval between administration of the drug and appearance of the side effects; presence of any alternative causes, well known side effects correlated to one or more substances, lessening and/or disappearance of the side effect due to reduction/suspension of the substance; reappearance of the side effect following re-administration of the drug; and on the basis of health care workers' observations.

Only the side effects that, regarding toxicity, could be correlated with the experimental treatment were taken into consideration (grade of correlation: possible, probable, certain) (Oken *et al.* 1982).

RESULTS

Statistical interpretation of the data

A clinical *investigation* (pilot study) was carried out on 55 patients affected by lymphoma, mainly recurrences or refractory, for a period of 5 years. The data collected were subjected to statistical evaluation and an intent to treat (ITT) survival curve was plotted, showing the start of treatment time on the abscissa and the survival percentage on the ordinate (see graph). The primary endpoint was the objective response rate (ORR) assessed by independent review. The secondary endpoints were the complete remission rate (CRR), the duration of the response, the progression-free survival (PFS), the overall survival (OS) and the safety and tolerability. At the time of the long-term follow-up analysis, the data allowed the following observations:

A complete response (CR) and stable disease (SD) was observed in 38 + 8 cases (84%). Nine cases (16%) were in progression (P) (Figure 2).

For the patients affected by LH, overall survival at 1, 3 and 5 years was 92%, 82% and 82% respectively, while for those with LNH it was 95%, 88% and 88% respectively (Figure 3). A complete response was achieved in 72% of cases and stability in 14%; 11% of cases were in progression (Figure 4).

Of the 17 patients with advanced disease stage (stage IV), all 17 achieved a complete response and are continuing the treatment. Seven of these patients received the treatment as first-line therapy (Table 3).

The survival curve (Intent To Treat) (Figure 5) shows that:

(a) after 12 months of treatment, approx. 96% of the patients were still alive;
(b) after 36 months of treatment, approx. 82% were still alive;
(c) at the end of the study (60 months), overall survival (OS) was approx. 80%
(d) the trend of the curve shows that significant number of deaths occurred in the first three years
(e) following treatment

No recurrence of the disease was observed in patients receiving the DBM as adjuvant therapy.

Performance status

A considerable improvement was observed in general symptoms, most notable in the patients who had not received previous treatment (chemo-, radiotherapy, corticosteroids). This made it possible for the patients to continue the treatment at home, carrying out their normal activities without any problems.

Tab. 3. DBM effectiveness in stage IV Lymphomas.

Stage IV (All)	Total	CR	PR	SD	PD
	17	10	1	4	2
Stage IV (Only DBM)	Total	CR	PR	SD	PD
	7	6	0	1	0

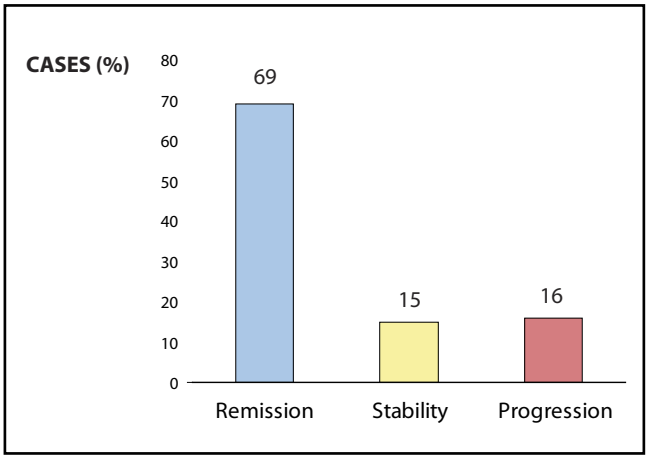

Fig. 2. Global effectiveness in Lymph-proliferative disorders with DBM.

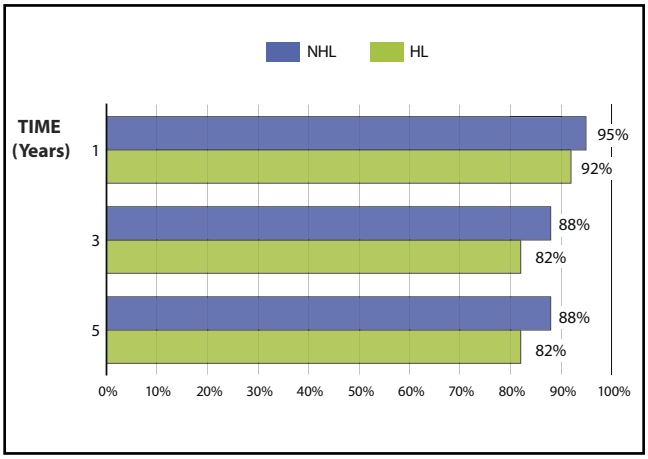

Fig. 3. Observed Survival in Lymph-Proliferative disorders with DBM treatment.

Side effects

The side effects due to the treatment were mild and transient (degrees 1–2) (Table 4). The majority were general symptoms, such as gastrointestinal disorders (diarrhoea, nausea) and mild drowsiness, probably due to the administration of somatostatin and melatonin respectively. These effects proved to be transitory, with adjustment of the dose and subsequent disappearance after around 6 months (min 4, max 12).

There were no deaths correlated with the pharmacological treatment (Table 4).

DISCUSSION

Molecules such as Somatostatin (SST), Prolactin (PRL), Retinoids, and Melatonin (MLT) are able to influence lymphoid growth (Sharma & Vinayak 2013; Sharma & Vinayak 2012; Paternoster *et al.* 2009; Bao *et al.* 2006; Bruemmer *et al.* 2003; Ashfaq *et al.* 2000; Brown *et al.* 1997; O'Neal *et al.* 1991; Persengiev & Kyurkchiev 1993; Abb & Deinhardt 1981), while the use of cyclophosphamide in lymphoproliferative disorders is well known in the haematological field.

The ubiquitary receptorial expression of PRL and of the growth hormone (GH) represents one of the direct and generalised aspects of the mitogenic role of these molecules. The powerful mitogenic role of GH and prolactin is known and widely documented;, the co-expression, interactivity and dimerization of the respective membrane receptor proteins (Matera *et al.* 2000; Pellegrini *et al.* 1992), and the fact that the proliferative index and the speed of progression of the neoplastic populations is directly proportional to the receptorial expression of GH itself. Cell proliferation is therefore strictly dependent on prolactin (Singh *et al.* 2006; Rillema *et al.* 1992; Russell & Laird 1989; Buckley *et al.* 1988; Davis & Linzer 1988; Gout *et al.* 1980), on GH (Hooghe *et al.* 1998), and on mitogenic molecules which are dependent on GH and positively regulated by it, such as Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), Hepatocyte Growth Factor (HGF), Insulin-like Growth factor (IGF), Nerve Growth Factor (NGF), Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor (TGF), and Vascular Endothelial Growth Factor (VEGF); as well as growth factors produced by the gastrointestinal system, such as Vasoactive Intestinal Peptide (VIP), Cholecystokinin (CCK) and Gastrin (G). (Matt *et al.* 2009; Trejo *et al.* 2004; Ferrara & Gerber 2002; Ornitz & Itoh 2001; Boonstra *et al.* 1995; Cos & Blask 1994; Comoglio, 1993; Lüscher *et al.* 1992; Heldin & Westermark 1991)

Both physiological and neoplastic cell proliferation take place thanks to these same molecules, which the neoplastic cells also use, but exponentially with respect to healthy cells. The loss of differentiation and uncontrolled proliferation, albeit to different extents, characterise all neoplasms. The use of somatostatin and its analogues, by acting on growth, the common denominator of all tumours, is thus a rational indication in all tumours (Ruscica *et al.* 2012; Tejeda *et al.* 2008).

A receptorial expression for somatostatin has been documented in many tumours, not just neuroendocrine forms (Hasskarl *et al.* 2011; Ferone *et al.* 2011; Keller *et al.* 2005; Dalm *et al.* 2004; Zhou *et al.* 2002; Oomen *et al.* 2000; Van den Anker-Lugtenburg *et al.* 1996; Lipp *et al.* 1995; Witzig *et al.* 1995; Reubi *et al.* 1992; Baschieri

Tab. 4. Adverse effects.

	CASES				Active Molecule	Grade correlation
	Grade 1		Grade 2			
	Nr	%	Nr	%		
Gastrointestinal						
Nausea/Vomiting	7	12.5	5	6	Somatostatin	Certain
Diarrhoea	13	75	9	8	Somatostatin	Certain
Neurological						
Drowsiness	7	12.5	–	–	Melatonin	Probable

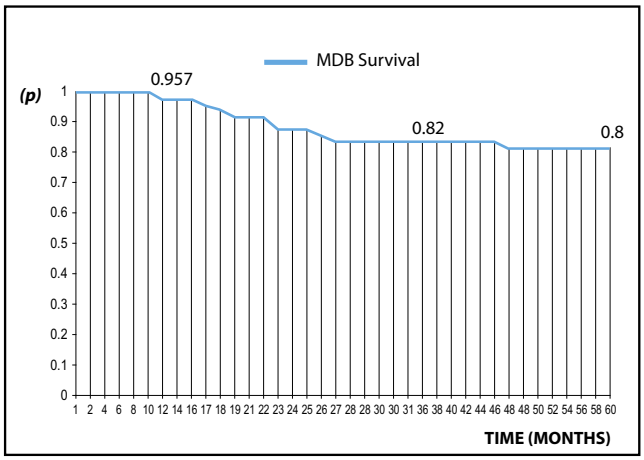

Fig. 4. DBM Effectiveness for NHL patients.

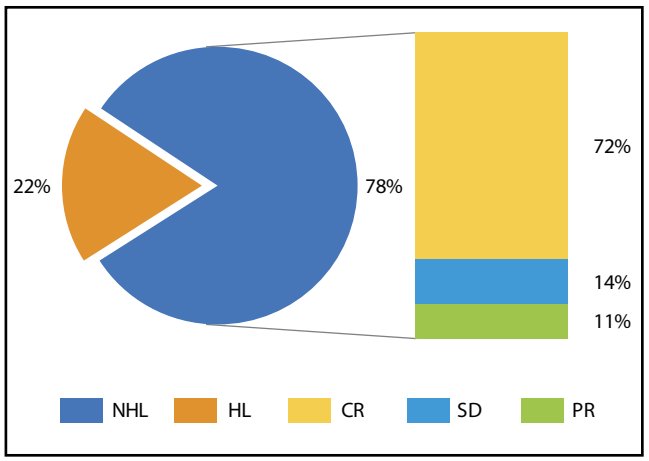

Fig. 5. Overall Survival (OS) with DBM in Lymphoproliferative Disorders. HL: Hodgkin's Lymphoma; NHL: Non Hodgkin's Lymphoma; RC: Complete Remission; SD: Stable Disease; PR: Progression.

et al. 1989; Jakobs & Schultz 1983). The causal and proportional relationship between the receptorial expression of GH (of which SST is the biological antidote) and tumour induction and progression have also been documented, using Molecular Biology (PCR, Western Blot) and histochemical techniques to reveal markedly higher concentrations of the Growth Hormone receptor (GHR) in tumour tissues compared to healthy tissues (Lin *et al.* 2011; Gebre-Medhin *et al.* 2001). It is now accepted that neoplastic progression is strictly dependent on angiogenesis and lymphogenesis, and that they represent an obligatory and essential stage of the disease (Aggarwal *et al.* 2012; Bergers & Benjamin 2003; Greenblatt & Shubi 1968). The acquisition of an angiogenic phenotype is decisive for the expansion of the tumour. Somatostatin and its analogues negatively regulate the "angiogenic inductors" and all the stages of angiogenesis such as the cascade of monocytes, interleukin 8 (IL-8), Prostaglandin E 2 (PGE2) and VIP, endothelial Nitric oxide synthase (e-Nos) (Ribatti *et al.* 2007; Dasgupta, 2004; Arena *et al.* 2004; Florio *et al.* 2003; García de la Torre *et al.* 2002) as well as the growth factors whose synergism is essential for angiogenesis, such as l VEGF-A TGF, FGF, HGF and PDGF (Chekhonin *et al.* 2012; Woltering, 2003). The inhibition of angiogenesis induced by SST is synergistically and factorially reinforced by the other components of the DBM, such as MLT, Retinoids, Vitamin D_3, Vitamin C, prolactin inhibitors (Dopaminergic agonists) and components of the extracellular matrix such as galactosamine sulphate. In the same way, the cytostatic, antiproliferative, and antimetastatic effect of Somatostatin is effectively synergized by the prolactin inhibitors (Cabergoline and Bromocriptine) and by the other components of the DBM such as Retinoids, MLT, Vitamin D_3 Calcium, Vit E, and Vit C. (Fujita *et al.* 2010; Singh *et al.* 2010; Trump *et al.* 2006; Trubiani *et al.* 2005; Chen *et al.* 2005; Guidoboni *et al.* 2005; Consolini *et al.* 2001; Dalen & Neuzil 2003; Darwiche *et al.* 2001; Lissoni *et al.* 2000; Sarna *et al.* 2000; Bode *et al.* 1999; Sundaresan *et al.* 1997; Yu *et al.* 1996,1997; Turley *et al.* 1995; Defacque *et al.* 1994; Drake *et al.* 2010; Hickish *et al.* 1993; Kao *et al.* 1993; Thomas & Hoffman 1989; Haverty *et al.* 1987).

This scientific evidence provided the rationale for carrying out a pilot study on the combined use of these components in patients affected by different forms of lymphoma.

The results of the study made it possible to confirm not only the already known anticancer activity of retinoids (Kempf *et al.* 2003; Younes *et al.* 2000; Knobler *et al.* 1991) and vitamins D3 and E in these lymphoproliferative diseases (Nieto-Rementería *et al.* 2009; Zhang *et al.* 2002; Drake *et al.* 2010), but also to detect a marked response in terms of quality of life and total absence of the often debilitating side effects that frequently occur with conventional oncological treatments. Phenomena such as Leukopenia (Schmitz *et al.* 2012), thrombocytopenia, and immunosuppression, attributed to the administration of massive doses of chemotherapy, are mild and often absent with the concomitant use of low doses (50 mg) of cyclophosphamide and molecules with a marked trophic and myeloprotective activity, such as MLT and Vitamins (Anwar *et al.* 1998; Heaney *et al.* 2008; Sarna & Bhola 1993; Prasad *et al.* 1992; Coleman *et al.* 2012; Prasad *et al.* 2010). This combination of drugs and the low dosage favours the alteration of the mechanism of action of the alkylating molecule from cytolytic to apoptotic, obtaining advantages both in pharmacological and Performance Status terms.

CONCLUSIONS

The main objective of this biological approach (DBM) is to safeguard and restore the biological microenvironment. The restoring action (homeostasis) is achieved by means of two-stage activity, reinforcing on one hand the ordered and physiological cell growth (differentiation) of healthy tissues in opposition to the uncontrolled and undistinguished (undifferentiated) growth of neoplastic tissues. These actions are completed by the antioxidising, free antiradical, prodifferentiating (reconversion of tumour or undifferentiated cells to normal), pro-apoptotic (inducing the tumour cell to cell death, with physiological, non-cytotoxic mechanisms), immunostimulating (Melatonin and Vitamins), antiproliferative (Melatonin, Somatostatin, prolactin inhibitors, Vitamins), and antimetastatic activity and, by means of direct and indirect mechanisms, the reinforcement of growth factor inhibition (Di Bella 2010).

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