Evaluation of an unconventional cancer treatment (the Di Bella multitherapy): results of phase II trials in Italy

Italian Study Group for the Di Bella Multitherapy Trials

Editorial by Müllner and p 268

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Abstract

Objective To determine whether the treatment known as Di Bella multitherapy exerts antitumour activity worthy of further controlled clinical evaluation.
Design 11 independent multicentre uncontrolled phase II trials relevant to 8 different types of cancer.
Setting 26 Italian hospitals specialising in cancer treatment.
Subjects 386 patients with advanced cancer were enrolled in the trials between March and July 1998 and followed to 31 October 1998.
Interventions Melatonin, bromocriptine, either somatostatin or octreotide, and retinoid solution, the drugs that constitute Di Bella multitherapy, were given to patients daily. Cyclophosphamide and hydroxyurea were added in some trials.
Main outcome measures Responses were assessed every 1, 2, or 3 months, depending on the specific trial, and toxicity was evaluated using criteria developed by the World Health Organisation.
Results No patient showed complete remission. Three patients showed partial remission: 1 of the 32 patients with non-Hodgkin's lymphoma; 1 of the 33 patients with breast cancer; and 1 of the 29 patients with pancreatic cancer. At the second examination, 12% (47) of the patients had stable disease; 52% (199) progressed; and 25% (97) died.
Conclusions Di Bella multitherapy did not show sufficient efficacy in patients with advanced cancer to warrant further clinical testing.

Introduction

In the past year there has been extensive international media coverage of the allegedly successful treatment in Italy of a number of malignant neoplasms with Di Bella multitherapy. This is a multidrug, custom made medical treatment developed by Luigi Di Bella, an Italian physician, who over the past 25 years has perfected and administered it on a private outpatient basis, claiming its effectiveness in blocking, if not curing altogether, most cancers. Over the past two years a number of associations have been created to support this treatment; these associations mounted a campaign to request that Di Bella multitherapy be included among those cancer treatments considered to be effective and that its cost thus be fully reimbursed by the Italian national health service. When requested by the ministry of health to submit scientific evidence of the effectiveness of Di Bella multitherapy, Dr Di Bella failed to produce any published scientific paper; therefore, the Italian national drug committee (the drug regulatory authority in Italy) denied approval. Following growing public demand, including public demonstrations, the national cancer advisory committee advised the minister of health to perform a series of uncontrolled phase II trials to test whether Di Bella multitherapy had any clinical efficacy.[1 2]

In February 1998 the Italian parliament passed an act authorising that clinical trials be conducted and making funds available for these trials[3]; the responsibility of coordinating the entire effort was entrusted to the Istituto Superiore di Sanità (the Italian national institute of health). The National Cancer Advisory Committee and Dr Di Bella agreed on the types of cancer to be included in the trials and the means of standardising the custom made drugs included in the therapy. It was agreed to develop 11 independent protocols for uncontrolled phase II trials on eight different types of advanced stage cancer. The specific types of cancer were selected on the basis of various factors, including anecdotal reports of successful treatment with Di Bella multitherapy, potential activity of some of the components of Di Bella multitherapy, and the lack of effective treatment for the specific cancer.

The objective of the trials was to determine whether Di Bella multitherapy exerts antitumour activity worthy of further controlled clinical evaluation (that is, phase III randomised controlled trials). The main end point of each trial was the objective response of reduction in tumour size. Here we present the final results of the uncontrolled phase II trials.

Patients and methods

Study protocols

The following types of cancer were studied: aggressive non-Hodgkin's lymphoma and chronic lymphoid leukemia in patients not eligible for chemotherapy or radiotherapy of proved efficacy; breast cancer in patients ⩾70 years of age who were eligible for surgery; stage IV breast cancer in patients previously treated with chemotherapy or endocrine therapy, or both, who had a performance status 0-2 according to the Eastern Cooperative Oncology Group (ECOG); stage IV breast cancer in patients not eligible for conventional chemotherapy or hormonal therapy (ECOG performance status 3-4); metastatic non-small cell lung cancer in patients who had had first line chemotherapy and in patients with no previous chemotherapy; advanced colorectal cancer in previously treated patients; advanced pancreatic carcinoma in patients without previous chemotherapy; metastatic or recurrent squamous cell head, neck, and oesophageal cancer in previously treated patients; recurrent glioblastoma after surgery and conventional radiotherapy; and advanced solid neoplasms (metastatic tumours originating from lung, oesophagus, stomach, pancreas, liver, colon, rectum, bladder, endometrium and cervix uteri, ovary) in terminally ill, untreatable patients. The trial involving breast cancer in patients who were eligible for surgery was discontinued after 2 months because only two patients were enrolled.

website *e*xtra

An additional table and a list of members of the study group can be found on our website

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Several thousand patients requested treatment with Di Bella multitherapy during January and February 1998. A waiting list of potentially eligible patients who had requested the treatment was created for each protocol. For the inclusion in the trials, patients were randomly selected from the waiting lists.

In each study, patients had to be at least 18 years of age, and they had to have measurable or assessable lesions, histological or cytological diagnosis of cancer, and no previous treatment with Di Bella multitherapy. Detailed information on the study protocols and on the eligibility criteria are available in two reports of the Istituto Superiore di Sanità[4 5] and, temporarily, on the internet at the site of the Istituto Superiore di Sanità (www.iss.it).

The change in tumour size was assessed after one, two, or three months, depending on the specific trial, and the treatment status and vital status of all patients was ascertained on 31 October. All trials were conducted according to the requirements of good clinical practice.

A network of 26 hospital cancer divisions selected by the steering committee of the study group administered the drugs and measured the tumours. The Istituto Superiore di Sanità coordinated the trials and supervised the production, purchase, and distribution of the drugs.

Components of treatment

Di Bella multitherapy consists of the daily administration of a combination of drugs: melatonin (20 mg), bromocriptine (2.5 mg), somatostatin (3 mg) or octreotide (1 mg), and a solution of retinoids (7 g). Hydroxyurea (1 mg/day) was added in the treatment of glioblastoma, and cyclophosphamide (50 mg/day) was added, with time of administration varying among trials, in the treatment of all other types of cancer studied, except for terminally ill patients, who represented the study populations of two trials (more severe breast cancer and advanced solid neoplasia). Ascorbic acid (1-2 g) and dihydrotachisterol (0.4-0.9 mg) were added to the treatment during April-May 1998, following Di Bella's specific recommendation. All drugs were given orally, except for octreotide (subcutaneous injection) and somatostatin (slow subcutaneous injection; 3 mg in 8 hours).

The retinoid solution was composed of all-trans retinoic acid (0.5 g), β carotene (2 g), axerophtholum palmitate (0.5 g), and α tocopheryl acetate (1000 g). The melatonin tablets consisted of melatonin-adenosine-glycine (2:9:5 mg/tablet). The melatonin tablets and the retinoid solution were prepared as required, following Di Bella's directions, by the Stabilimento Chimico Farmaceutico Militare (military pharmaceutical chemical plant) in Florence in compliance with good manufacturing practices; each batch was subject to quantitative and qualitative control by the Istituto Superiore di Sanità. The other drugs included in the regimen are marketed in Italy and were provided by pharmaceutical companies.

Study size

With the exception of trial on glioblastoma, which used Simon's two stage optimal design,[6] the trials used a one stage design because it was thought that a sufficient number of patients could be enrolled in a very short period. For each trial, a sample size that would discriminate between p_0 (insignificant activity) and p_1 (activity worthy of further clinical trials) with a 5% probability of type I error and a 5% probability of type II error was determined. The values for p_0 and p_1 were established independently for each trial and varied from 5% to 10% for p_0 and from 20% to 30% for p_1. Based on these elements, the minimum number of responses that would be needed to consider the regimen as worthy of further study was calculated for each trial protocol. For a minimum number of responses ranging from 2 to 12, the number of patients needed for each trial was between 24 and 69.

Analysis

The primary analysis included all patients who fulfilled the major eligibility criteria. The proportion of patients responding to treatment was the end point for all trials. Responses were evaluated according to the criteria of the World Health Organisation.[7] A complete response was defined as the disappearance of all known disease (determined by two observations not less than four weeks apart); a partial response was defined as a decrease in tumour size ⩾50% (determined by two observations not less than four weeks apart); for patients with chronic lymphoid leukaemia, peripheral blood count and the bone marrow picture were considered. Each patient was classified according to the best response observed during follow up; patients whose disease showed no signs of progression between any two observations were classified as stable. The lesions were measured (by clinical examination, *x* ray, computed tomography, etc) every 1, 2, or 3 months. An independent end point evaluation committee (consisting of radiologists, oncologists, and haematologists) did a blind review of the clinical records and documents available for each patient to corroborate the evaluation made by the participating hospitals. Patients with early progression and those who died, as well as patients who discontinued treatment because of toxicity, were included in the analysis of clinical outcome. Adverse events were evaluated and graded on the basis of the WHO toxicity criteria.[7]

The trial protocols were approved by an ad hoc national ethics committee and by the ethics committees of each hospital; patients were required to provide written informed consent.

Each trial was monitored by a clinical monitor. All clinical sites were audited by the Istituto Superiore di Sanità.

Results

Between March and July 1998, 395 patients were enrolled in the trials. Nine of these patients were excluded because they did not meet major eligibility criteria; thus 386 patients were included in the analysis. Table 1 shows selected characteristics of each trial's study population.

The main results of each trial are presented in table 2. None of the patients showed a complete response. Three showed partial responses: one patient with non-Hodgkin's lymphoma, one patient with less severe breast cancer, and one patient with pancreatic cancer.

Table 1 Characteristics at baseline of 386 patients included in trials* of Di Bella multitherapy. Values are numbers of patients unless otherwise stated

Characteristic	Lymphoma (n=32)	Lymphoid leukaemia (n=22)	Breast cancer: Less severe (n=33)	Breast cancer: More severe (n=34)	Lung cancer: Treated (n=65)	Lung cancer: Untreated (n=51)	Colorectal cancer (n=34)	Pancreatic cancer (n=29)	Head and neck cancer (n=32)	Glioblastoma (n=20)	Advanced neoplasms (n=34)
No of women	13	7	33	34	12	7	21	12	3	10	24
Median age (years)	58	62	54	59	62	67	63	69	62	61	70
Median No of months from diagnosis	34	62	78	58	12	3	21	3	34	10	14
Previous treatment:											
Surgery	8	3	30	31	23	17	34	19	22	20	21
Chemotherapy	32	22	31	32	65	—	34	—	32	—	23
Hormone therapy	—	—	27	29	—	—	—	—	—	—	2
Radiotherapy	13	1	23	26	39	12	10	2	30	20	5
ECOG performance status:											
0	7	15	13	—	8	12	11	10	1	—	—
1	8	4	13	1	34	30	12	14	14	6	—
2	7	2	7	1	23	9	11	5	17	14	3
3	10	1	—	25	—	—	—	—	—	—	10
4	—	—	—	7	—	—	—	—	—	—	21

*Names of trials have been abbreviated in tables. More accurately, the trials were: non-Hodgkin's lymphoma; chronic lymphoid leukaemia; metastatic breast cancer (less (ECOG performance status 0-2) or more severe (performance status 3-4)); metastatic non-small cell lung cancer, patients previously treated or not previously untreated with chemotherapy; advanced colorectal cancer; advanced pancreatic cancer; head, neck, and oesophageal cancer, metastatic or locally advanced; glioblastoma, recurring after surgery and external radiotherapy; advanced solid neoplasms among terminally ill, untreatable patients.

At the second examination, 47 (12%) patients had stable disease, in 199 patients (52%) disease had progressed, and 97 (25%) had died. In individual trials the proportion of patients whose cancer progressed ranged from 38% to 70%, and the proportion of deaths ranged from 0% to 44%. Thirty two patients (8%) discontinued the experimental treatment because of toxicity or reasons not related to drug treatment.

Treatment status and survival of the patients at 31 October 1998 (last date of follow up) are shown on the *BMJ*'s website. Overall, 16 (4%) patients were still receiving treatment; 129 (33%) patients were not receiving treatment; 219 (57%) patients had died; and 22 patients (6%) were lost to follow up. The 16 patients who were still receiving Di Bella multitherapy comprised three patients with a partial response and 13 patients with stable disease.

All 395 patients enrolled in the trials were evaluated for toxicity. During the observation period (on average, each patient was treated for 2 months), 157 (40%) patients had a total of 273 drug side effects (any grade of severity) associated with treatment, of which 64 events (in 41 (26%) patients) were classified as "severe" (WHO grade 3-4). The proportion of adverse events ranged from 5% among patients with glioblastoma to 77% among patients with chronic lymphoid leukaemia. Patients with lung cancer and glioblastoma who had not previously had chemotherapy had no severe events, whereas more than one third of the patients with chronic lymphoid leukaemia had a severe event. Most of the adverse events (157) were of gastrointestinal nature: diarrhoea, vomiting, and nausea. Somnolence was seen in 31 patients. In the trials including cyclophosphamide, 30 cases of blood related toxicity (anaemia, thrombocytopenia) were seen. All of these adverse events were to be expected on the basis of the pharmacological properties of the various drugs and had been described in the

Table 2 Best response between examinations of cancer patients given Di Bella multitherapy

Trial*	Months between examinations	Partial response	Stable disease	Progressive disease	Died	Treatment discontinued†	Not assessable	Total
Lymphoma	1	1	8	17	6	0	0	32
Lymphoid leukaemia	2	0	8	10	0	4	0	22
Breast cancer:								
Less severe	2	1	4	23	4	1	0	33
More severe	2	0	4	14	10	6	0	34
Lung cancer:								
Treated	1	0	1	28	29	4	3	65
Untreated	1	0	6	27	13	4	1	51
Colorectal cancer	2	0	3	21	2	7	1	34
Pancreatic cancer	3	1	6	13	8	1	0	29
Head and neck cancer	2	0	3	19	7	3	0	32
Glioblastomas	3	0	2	14	4	0	0	20
Advanced neoplasms	2	0	2	13	14	2	3	34
Total		3	47	199	97	32	8	386
% (95% CI)		0.8 (0.2 to 2.25)	12.2 (9.1 to 15.9)	51.6 (46.4 to 56.6)	25.1 (20.9 to 29.8)	8.3 (5.7 to 11.5)	2.1 (0.9 to 4.0)	100

*See footnote to table 1.
†Discontinued for toxicity or other reasons.

investigators' brochure (which contained details of previous knowledge about the drugs under investigation).

Discussion

The results of these trials indicate that Di Bella multitherapy does not have sufficient efficacy in advanced cancer to warrant further clinical testing. The three cases of partial response among the 386 patients represent a 0.8% response rate, which is well below any reasonable threshold for declaring that a new regimen shows promise.

These low response rates seem to rule out the possibility that the entire regimen has any effect over and above the moderate activity already seen for some of its components. Objective responses in patients treated with somatostatin or its analogues have been described in phase II trials in pancreatic, colorectal, and breast cancer.[8] Retinoids are being extensively studied in several haematological and solid malignancies, with results that range from little or no effect to the spectacular success obtained in acute promyelocytic leukaemia, where all-trans retinoic acid induces complete remission in a high proportion of patients.[8] Cyclophosphamide is one of the most widely used anticancer drugs, as a single agent or in combination chemotherapy regimens, and it is active in many haematological and solid malignancies, including breast cancer and non-Hodgkin's lymphoma.[8] The 50 mg of cyclophosphamide daily that was used in the multitherapy regimen is not much lower than the dose commonly used in chemotherapy.

Overall, the results of these trials fail to justify the use of Di Bella multitherapy and they even suggest that it may be associated with considerable toxicity. Furthermore, the observation that Di Bella multitherapy was discontinued after several months in 85% of the patients because of progression, toxicity, or death means that this treatment is unlikely to be effective in the long term.

As in most phase II trials, the eligibility criteria restricted the enrolment to patients who could not receive standard treatments, since it would have been unethical to withdraw from patients treatments of known efficacy. However, only two trials (more severe breast cancer, and solid neoplasms among terminally ill patients) focused on critically ill patients; in all other trials, most patients had a fair to good performance status. Terminally ill patients were included because of the increasing number of court orders for terminal cancer patients to be given Di Bella multitherapy, but the results of these two trials show that the treatment neither cures nor stops the progression of tumours in patients with terminal cancer.

Eighty patients who had not had previous chemotherapy were enrolled in two of the trials. Only one pancreatic cancer patients showed any response, and no response was seen in lung cancer patients who had not previously had chemotherapy.

The trials, with their rigid treatment protocols, did not reproduce one element of the method that Di Bella claims is crucial: tailoring the treatment to individual patients. Unfortunately, no trial can be conducted without a treatment protocol, and details on the criteria followed by Di Bella and his disciples when adjusting the treatment have not been released. Therefore, it cannot be ruled out that better results could have been obtained by modulating treatment. However, in all trials the protocols followed written indications provided by Di Bella. Furthermore, the potential for widespread use of a new treatment is greatly reduced if its effectiveness depends on the doctor's ability to modulate it and no explicit criteria are available.

Key messages

- A treatment known as Di Bella multitherapy was widely prescribed in Italy to treat most types of cancer despite lack of scientific evidence
- Eleven independent multicentre uncontrolled phase II trials relevant to eight different types of advanced cancer were conducted
- None of the 386 patients enrolled in the trial showed a complete response; three patients showed a partial response
- This regimen does not have sufficient activity in advanced cancer to warrant further clinical testing

The Di Bella multitherapy has been widely prescribed in Italy despite lack of scientific evidence. Given the high mortality from cancer, it is not surprising that thousands of people continue to seek unconventional treatments. Although claims of "wonder drugs" are occasionally reported by the media, public expectation in this case reached unprecedented levels in Italy.

Phase III randomised controlled trials (which were intended as a further step if results were positive) would not have been feasible for both ethical and practical reasons. On the one hand, preliminary evidence about the antitumor activity of Di Bella multitherapy was lacking and, on the other, patients who were seeking this treatment would have hardly agreed to be randomly allocated to different treatments. These uncontrolled phase II trials, which were planned, conducted, and concluded in less than 10 months, have given the Italian scientific community a solid base for the ongoing debate. We believe that this approach was the best way to cope with an unconventional treatment that was gaining widespread public acceptance in the absence of scientific evidence.

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Contributors: Members of the Italian Study Group for the Di Bella Multitherapy Trials are listed on the *BMJ*'s website. The protocol design of the studies was carried out by the principal investigators. Each member of the steering committee* took

responsibility for the study design, the supervision of the study, the discussion of the results, and the revision and approval of the final version of the paper. Members of the research coordinating centre contributed to the final version of protocols, coordinated all phases of the study, participated in data collection, carried out the analysis and interpretation of data, and revised and approved the final version of the paper. Members of the editorial committee wrote the paper and act as guarantors.

*Dr G Di Bella, the son of Dr L Di Bella, participated at only the first two meetings of the Steering Committee. On many occasions, he strongly disagreed with the performance and results of the trials. No part of the present article has been discussed or agreed with Dr G Di Bella.

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Workplace bullying in NHS community trust: staff questionnaire survey

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Abstract

Objectives To determine the prevalence of workplace bullying in an NHS community trust; to examine the association between bullying and occupational health outcomes; and to investigate the relation between support at work and bullying.

Design Questionnaire survey.

Setting NHS community trust in the south east of England.

Subjects Trust employees.

Main outcome measures Measures included a 20 item inventory of bullying behaviours designed for the study, the job induced stress scale, the hospital anxiety and depression scale, the overall job satisfaction scale, the support at work scale, and the propensity to leave scale.

Results 1100 employees returned questionnaires—a response rate of 70%. 421 (38%) employees reported experiencing one or more types of bullying in the previous year. 460 (42%) had witnessed the bullying of others. When bullying occurred it was most likely to be by a manager. Two thirds of the victims of bullying had tried to take action when the bullying occurred, but most were dissatisfied with the outcome. Staff who had been bullied had significantly lower levels of job satisfaction (mean 10.5 (SD 2.7) *v* 12.2 (2.3), $P < 0.001$) and higher levels of job induced stress (mean 22.5 (SD 6.1) *v* 16.9 (5.8), $P < 0.001$), depression (8% (33) *v* 1% (7), $P < 0.001$), anxiety (30% (125) *v* 9% (60), $P < 0.001$), and intention to leave the job (8.5 (2.9) *v* 7.0 (2.7), $P < 0.001$). Support at work seemed to protect people from some of the damaging effects of bullying.

Conclusions Bullying is a serious problem. Setting up systems for supporting staff and for dealing with interpersonal conflict may have benefits for both employers and staff.

Introduction

Bullying in the workplace has been recognised as an important issue by trade unions in Britain for about five years. Several reports have graphically illustrated the pain, mental distress, physical illness, and career damage suffered by victims of bullying,[1–4] but academic study began only recently.[5–7] The most developed research comes from Scandinavia,[8–12] where there is strong public awareness, government funded research, and established anti-bullying legislation.

Bullying presents considerable methodological problems for researchers. A central difficulty is that of definition as no clear consensus exists on what constitutes adult bullying. Although physical bullying is rarely reported, the workplace presents opportunities for a wide range of intimidating tactics. Rayner and Hoel provide five categories of bullying behaviour.[7] These are threat to professional status (for example, belittling opinion, public professional humiliation, accusation of lack of effort); threat to personal standing (for example, name calling, insults, teasing); isolation (for example, preventing access to opportunities such as training, withholding information); overwork (for example, undue pressure to produce work, impossible deadlines, unnecessary disruptions); and destabilisation (for example, failure to give credit when due, meaningless tasks, removal of responsibility, shifting of goal posts).

Most definitions of workplace bullying share three elements that are influenced by case law definitions in the related areas of racial and sexual harassment. Firstly, bullying is defined in terms of its effect on the recipient not the intention of the bully. Thus it is subject to variations in personal perceptions. Secondly, there must be a negative effect on the victim.[7 8] Lyons and colleagues use the following definition: "persistent, offensive, abusive, intimidating, malicious or insulting behaviour, abuse of power or unfair penal sanctions, which makes the recipient feel upset, threatened, humiliated or vulnerable,