Results from a Historical Survey of the Survival of Cancer Patients Given Di Bella Multitherapy

Eva Buiatti, M.D.1
Stefania Arniani, M.S.2
Arduino Verdecchia, Ph.D.3
Lorenzo Tomatis, M.D.4
and the Italian Cancer Registries5

1 Epidemiology Unit, Direzione Sanitaria Azienda USL Firenze, Florence, Italy.
2 Centro di Documentazione per la Salute, Regional Health Service, Regione Emilia Romagna, Italy.
3 National Institute of Health, Epidemiology and Biostatistics Branch, National Institute of Health, Rome, Italy.
4 Istituto per l’Infanzia Burlo Garofalo, Direzione scientifica, Trieste, Italy.
5 Cancer Registries of Piedmont, Veneto, Trieste, Liguria, Lombardy, Parma, Modena, Ferrara, Romagna, Macerata, Latina, and Ragusa; the National Bone Cancer Registry in the Rizzoli Institute, Bologna; and the National Task Force for Pediatric Oncology (FONOP), Italy.

BACKGROUND. The Italian media have given wide coverage to a number of successes in treating cancer patients with an alternative therapy developed by Dr. Luigi Di Bella, a physician in Modena, Italy. In 1998, the Ministry of Health, under considerable pressure from the public, decided to promote studies to evaluate its efficacy.

METHODS. Follow-up was conducted for cancer patients previously treated during the years 1971–1997 by Dr. Di Bella and registered in his archive. Identified cases were searched in cancer registries for diagnostic confirmation, date of diagnosis, and follow-up. Survival was compared with that in individually matched cancer cases derived from a pool of Italian cancer registries (the ITACARE data base). Kaplan–Meier survival curves were produced for all adult cancer patients as well as for children with leukemia and, in the matched analysis, for patients with cancer at the major anatomic sites and for all cancer patients combined. The homogeneity of survival curves between the two groups was tested by means of the log rank test.

RESULTS. After several exclusions, 314 patients were entered into the study. Follow-up was completed for 79%. Only four patients received Di Bella Multitherapy (MDB) as their only anticancer therapy. Of these, only 1 is still alive 2 years after diagnosis. Five-year survival rates for children with leukemia and adult cancer patients were both 29.4%. Five-year survival was significantly lower in comparison with ITACARE cases for patients with childhood leukemia, breast carcinoma, and adult leukemia, and for all cancer patients combined. Twenty-seven MDB patients survived 10 years or longer after diagnosis. In only three cases was this long survival unexpected.

CONCLUSIONS. The results for this series did not give any evidence that MDB improved the survival of the cancer patients. [See editorial on pages 1887–9 and commentaries on pages 1900–2 and 1903–11 this issue.] Cancer 1999;86:2143–9. © 1999 American Cancer Society.

KEYWORDS: alternative anticancer therapy, retrospective study, cancer survival, miracle cancer therapies.

Proposals of “miracle” cancer therapies without scientific evidence of effectiveness have been advanced numerous times in many different countries.1,2 Some of these have found the enthusiastic support of the local public and press. Recently, the Italian media have given wide coverage to a number of successes in treating cancer patients with an alternative therapy developed by Dr Luigi Di Bella, a physician in Modena, Italy. According to Dr. Di Bella, the therapy (known as Di Bella Multitherapy, or MDB) is a cocktail of somatostatin (or its synthetic equivalent octeotride), melatonin, a suspension of β-carotene, α-tocopherol and retinoic acid, bromocriptine, cyclophosphamide in low doses, vitamin D, and ascorbic acid.3 Dr. Di Bella...
is reported to have successfully treated about 10,000 cancer patients on a private outpatient basis. In Italy, many physicians, mostly general practitioners, are known as “MDB followers” and currently administer his therapy to cancer patients. However, a request from the Italian Ministry of Health to produce documentation on Dr. Di Bella’s patients yielded only 39 clinical records, none of which reported convincing evidence of success. Information on the “Di Bella case” has been given by the scientific press. In January 1998, the Ministry of Health, under considerable pressure from the public, decided to initiate a series of Phase II clinical trials and undertake a historical survival study of patients treated by Dr. Di Bella. Results from the historical study are presented herein.

MATERIALS AND METHODS

This study was possible thanks to the collaboration of Dr. Di Bella, who allowed access to the archive of clinical records of patients treated in Modena. In 1991–1992, brief individual information on previous patients of Dr. Di Bella’s was computerized by his collaborators. Thereafter, new cases were systematically added to the data base until June 1997. This data base matches the paper archive in nearly 100% of the cases. Computerized information is limited to identification number, first name and surname, date of birth, place of residence, and type of disease, with a varying degree of accuracy. However, through the identification number it is possible to identify for each subject the paper file with further personal and clinical information. The quality of this documentation varies, ranging from a full report on diagnostic and therapeutic procedures to incomplete handwritten notes.

The computerized data set was used to identify cancer cases. These were then searched in the archives of the population cancer registries active in Italy, with the aim of verifying the following information: date of incidence, cancer diagnosis (cancer site and histologic type), and life status.

The study included all patients with a cancer diagnosis resident in an area in which a population-based cancer registry was active or where follow-up by cancer registries was possible. Furthermore, for all childhood leukemia and bone primary cancers, information was searched independently from residence from the national bone cancer registry (Rizzoli Institute, Bologna) and from the national task force for pediatric oncology (FONOP). The records in the study base were 3076, referring to patients from the beginning of 1971 to June 1997.

Patients with a diagnosis different from malignant neoplasm or without diagnosis (n = 565 and n = 988, respectively, total = 1553, 50.5%) were excluded, leaving 1523 possible neoplastic cases. All those who resided in areas not covered by cancer registration and follow-up were also excluded (n = 918), with the exception of those with childhood leukemia and bone neoplasms. This exclusion, based on place of residence, was expected not to bias results for the effect of MDB.

The individual paper files for the remaining 605 patients were reviewed by one of us (E.B.). In 291 cases (48.1%) the file did not contain any documentation on MDB. These were excluded from the study.

The end of follow-up for the remaining 314 patients was March 30, 1998.

Information searched for each patient was as follows:

- Date of incidence;
- Diagnosis, histologic type, diffusion of the disease at diagnosis (in a subset);
- Treatment other than MDB (classified as surgical therapeutic, surgical palliative, medical, radiologic, other);
- Date of first contact with Dr. Di Bella;
- Drugs prescribed within MDB;
- Date of last contact with Dr. Di Bella;
- Life status at the end of follow-up.

All this information was searched in the individual paper files in the Di Bella archive and in the corresponding cancer registry files. Life status, when missing, was also sought at the municipality of last residence. When information was available from more than one source and it was discordant, the one from the cancer registry was used. Follow-up was completed for 248 patients (79%). The status of the records reviewed in the study is summarized in Figure 1. Kaplan–Meier survival curves were produced for all cancers combined in adults and for childhood leukemia.

In the ITACARE data base (a pool of Italian cancer registries), all cancers registered in Italy from the beginning of cancer registries’ activities to 1992 are recorded anonymously. A matching with up to four randomly selected cases from the ITACARE data base was attempted for each MDB patient, with the aim of comparing observed survival with the one of Italian registries’ cancer cases.

Matching criteria were defined as follows:

- Cancer occurrence in the same site and subsite (four-digit International Classification of Diseases, 9th revision [ICDIX] code);
• Same gender;
• Age within the 5-year age class (10-year age class for less frequent cancer sites) to which the MDB patient belonged;
• Period of diagnosis within 1.5 years (3 years for less frequent cancer sites);
• Alive at the first date on which the MDB patient entered MDB therapy.

Patients with relevant information missing (8%) were excluded from matching as well as those with a benign condition, uncertain tumor behavior, or tumor site unspecified (8%). Furthermore, matching was unsuccessful for 13% of patients, essentially those affected by uncommon cancers. The final number of patients included in this analysis was 176. For 152 patients 4 cases were matched, and for the remaining 24 patients 1–3 were matched (on average, 2.1 cancer cases for each patient). Results are presented for the whole set of 176 MDB patients fully or partially matched.

Survival estimates were obtained by means of the Kaplan–Meier method applied to the survival data for the MDB group of patients and the control group of cases selected from the ITACARE data base, for the cancer sites involved and for their combination. Testing homogeneity of survival curves over the two groups was done by means of the log rank test.

**RESULTS**

**Description of MDB Therapy and Patients**

Only 4 patients were treated with MDB as the first or only therapeutic choice. These were as follows:

• One patient with chronic myeloid leukemia diagnosed in 1978 at age 31 years, who died in August 1981;
• One patient with liver adenocarcinoma diagnosed in November 1990 at age 65 years, who died in May 1991;
• One patient with colorectal adenocarcinoma (of the ileocecal valve, with possible hepatic metastases at diagnosis) diagnosed in November 1994 at age 47 years, who died in November 1995;
• One patient with lung carcinoma clinically diagnosed in March 1996 at age 75 years, alive at the end of follow-up (March 1998).

All other patients underwent antineoplastic treatment (mostly surgery and chemotherapy) before beginning MDB, and some of them did not interrupt it during MDB.

The actual drugs prescribed as MDB changed widely during the period. Somatostatin, claimed by Dr. Di Bella to be essential, was used systematically only since 1989 (none before 1979, then increased progressively to 80% of patients). Only melatonin was used for 90% of the patients during the whole period,
while the suspension of provitamins and vitamin derivatives was used for most patients only during the past decade (2% of patients in 1971–1979, 70% in 1989–97). Cyclophosphamide, which was also said to be essential, was used to treat 20% of the patients in the first years (1971–1979) and 50% of patients in the remaining period. Bromocriptine, ascorbic acid, and vitamin D were never used in more than 50% of the cases. The number of drugs prescribed to each patient varied from 2 to 14.

In Table 1 the distribution of patients according to age and gender is shown. Children numbered 43 (making up 17.3% of the cases); almost all children (84%) began MDB in the first period (1971–1984).

In Table 2, the cancer sites represented by 10 cases or more are listed by the period in which MDB was begun (1971–1984, 1985–1997). Among childhood cancers, 39 (91%) had acute leukemia. The other childhood cancers were 1 Hodgkin disease (HD), 2 non-Hodgkin lymphomas (NHL), and 1 brain cancer. Among adults, the most frequent cancer was chronic leukemia (28), followed by lung carcinoma (19), female breast carcinoma (15), and acute leukemia (15). Twenty-six chronic leukemia patients out of 28 and 12 of 15 acute leukemia patients began treatment in the first period, when somatostatin was not used. The category “other sites” (n = 108) contained stomach neoplasms (n = 9), brain neoplasms (n = 8), malignant neoplasms not otherwise specified (n = 10), NHL (n = 7), HD (n = 5), and neoplasms of uncertain malignancy (n = 16).

The follow-up period varied from 9 months to 27 years. Overall, 52 of 248 patients were alive in March, 1998.

Table 3 shows the probability of survival after 1, 3, 5, and 10 years from diagnosis for childhood leukemia (39 patients) and for all adult cancers combined. Adult cases of uncertain malignancy or with relevant information missing were excluded from the analysis; thus, 181 subjects were analyzed.

For children, the survival probability was 29.4% after 5 years and 19.6% after 10 years. Only one case of childhood leukemia was treated with somatostatin.

For adults, at 5 years after diagnosis, the survival probability was 29.4% (16.0% after 10 years). Subdividing cases into 2 periods of MDB treatment (1971–1984 and 1985–1997) survival curves were similar. As previously mentioned, only in the second period was somatostatin used systematically.

Twenty-seven patients survived 10 years or more from the incidence date, and 20 from the first MDB date. The 20 cases were as follows:

- Seven childhood acute leukemia cases, diagnosed in 1971, 1973 (4 cases), 1974, and 1976. MDB was initiated an average of 1 year after the beginning of chemotherapy. In many cases, the two therapies continued simultaneously or in alternation. MDB lasted from 2 to 12 years.
- Two adult acute leukemia cases (ages 16 and 65 years). Both underwent chemotherapy, and one radiotherapy as well. For one, poor health conditions determined the choice of interrupting chemotherapy in favor of MDB.

### Table 1

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Missing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–14</td>
<td>15–64</td>
<td>65+</td>
</tr>
<tr>
<td>Males</td>
<td>22</td>
<td>76</td>
<td>28</td>
</tr>
<tr>
<td>Females</td>
<td>21</td>
<td>74</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>150</td>
<td>48</td>
</tr>
</tbody>
</table>

MDB: Di Bella Multitherapy.

### Table 2

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Period of MDB</th>
<th>Missing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon-rectum</td>
<td>1971–1984</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Lung</td>
<td>1971–1984</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Female breast</td>
<td>1971–1984</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Multiple</td>
<td>1971–1984</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Adult acute leukemia</td>
<td>1971–1984</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Chronic leukemia</td>
<td>1971–1984</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Adults, other sites</td>
<td>1971–1984</td>
<td>15</td>
<td>108</td>
</tr>
<tr>
<td>Childhood leukemia</td>
<td>1971–1984</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td>Children, other sites</td>
<td>1971–1984</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>1971–1984</td>
<td>119</td>
<td>248</td>
</tr>
</tbody>
</table>

MDB: Di Bella Multitherapy.

### Table 3

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Yrs from diagnosis</th>
<th>Survival probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood leukemia</td>
<td>1 3 5 10</td>
<td>85.3 47.0 29.4 19.6</td>
</tr>
<tr>
<td>Adult cancers</td>
<td>181</td>
<td>71.7 43.9 29.4 16.0</td>
</tr>
</tbody>
</table>

MDB: Di Bella Multitherapy.
Four chronic leukemia patients, of whom 3 died 20, 24, and 25 years after diagnosis. For the patient still alive (age 57 years in 1997), MDB was limited to melatonin. All were treated with chemotherapy.

Four malignancies with very poor documentation, not confirmed at the cancer registry.

Three patients who died after more than 10 years (1 with stomach cancer, 1 with vulvar adenocarcinoma, and 1 with adenocarcinoma of the sigmoid colon). All were treated with surgery and chemotherapy, successfully for the vulvar adenocarcinoma patient.

Of the 7 additional patients who survived 10 years or more since first diagnosis, 4 died less than 3 years after beginning MDB, and 2 chronic lymphatic leukemia patients died of their disease 8 years after beginning MDB. Three (1 with LH, 1 with surgically treated ovarian carcinoma, and 1 with surgically treated endometrial carcinoma) are still alive. They began to receive MDB in 1989, 1996, and 1991.

**Comparison of MDB Patients’ Survival with the Survival of ITACARE Cancer Patients**

The matching of MDB patients with ITACARE cases was effective for all matching variables. Date of incidence was slightly more recent in cases of MDB colorectal carcinoma (1990, standard deviation [S.D.] 4.8, vs. 1986, S.D. 1.9) and slightly longer ago for patients with MDB childhood leukemia (1975, S.D. 6.0, vs. 1979, S.D. 3.3) in comparison with the ITACARE control group.

Table 4 presents product limit survival estimates for cancer patients, both for the MDB group of patients and for the ITACARE control group of cases (conditional to the matched controls’ being alive at the start of MDB therapy), by cancer site and by all cancers combined. MDB patients showed lower survival probability over both the short term and the long term for all the cancer sites considered. Differences were statistically significant for cancers amenable to treatment, such as breast carcinoma, adulthood leukemia, childhood leukemia, and all cancers combined. Conversely, differences were smaller and not significant for lung and colorectal carcinoma. Dramatically low survival rates for childhood leukemia patients who received MDB compared with the ITACARE control group were shown.

Figure 2 shows cumulative survival for MDB patients (all cancers combined) and for the ITACARE control group. Over the long term, the ITACARE control group showed a twofold higher probability of survival compared with MDB patients.

In Figure 3, the same analysis is shown for childhood leukemia. The majority of childhood leukemia cases in Italy are treated in specialized hospitals with standardized protocols. In the period under examina-

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>No. of cases</th>
<th>MDB 1-yr</th>
<th>MDB 5-yr</th>
<th>ITACARE 1-yr</th>
<th>ITACARE 5-yr</th>
<th>Log rank $\chi^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast</td>
<td>14</td>
<td>55</td>
<td>23*</td>
<td>97</td>
<td>85</td>
<td>35.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lung</td>
<td>14</td>
<td>24</td>
<td>0</td>
<td>39</td>
<td>14</td>
<td>1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Colon-rectum</td>
<td>11</td>
<td>68</td>
<td>34</td>
<td>73</td>
<td>64</td>
<td>1.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Leukemia</td>
<td>65</td>
<td>60</td>
<td>26</td>
<td>80</td>
<td>51</td>
<td>14.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Childhood leukemia</td>
<td>32</td>
<td>42</td>
<td>21</td>
<td>87</td>
<td>70</td>
<td>39.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>All cancers</td>
<td>176</td>
<td>56</td>
<td>21</td>
<td>78</td>
<td>49</td>
<td>45.9</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* Two-year survival, because observations were censored after 2 years.
tion, the prognosis for patients with this neoplasm tended to be good. For MDB patients, the long term survival of children is similar to that shown for adult patients with acute leukemia. However, long term survival is far better for the ITACARE control group, as generally shown in population-based estimates.15

DISCUSSION
The number of cancer patients in this study is much smaller (1523) that the group reported by Dr. Di Bella (10,000). For approximately 48% of a nonselected 50% subsample of these patients, MDB treatment was not documented. A large number of cancer patients came in contact with Dr. Di Bella after June 1997, following the media attention he received. However, for these patients there is no accessible documentation and the follow-up is too short for survival evaluation.

The MDB protocol proposed by Dr. Di Bella does not correspond to his prescriptions in the period 1971–1997. Only melatonin was used systematically during the whole period.

A very limited number of patients underwent MDB as a first choice (4 of 314). Of these, 2 died after 1 year or less; 1 with chronic myeloid leukemia died after 4 years; and for the last patient, who is still alive after 2 years of follow-up, there is no histologic confirmation.

Survival probability for childhood leukemia was very poor in this series. Furthermore, only 7 patients of 39 with 10 years or more of follow-up (18%) could be considered recovered. When survival was compared between a subset of these cases and a sample of matched cases of childhood leukemia from Italian cancer registries, the difference in 5-year survival between the 2 series was highly significant. This bad result could be due to a selection of less curable cases in the Di Bella series, less frequent compliance on the part of these patients to chemotherapy and other therapies, or a combination of these two causes. Survival was also quite poor for the adult cancer patients.

Worse 5-year survival for the Di Bella series was found for those adult cancer patients for whom comparison was possible, significantly so for cancer sites in which therapy is known to be effective in prolonging survival.

Comparison is based on a nonbiased sample of cases derived from a pool of Italian cancer registries. Survival in this series is representative of the one in the period under consideration, being comprehensive of cancers at all stages and of areas with variable therapeutic quality.15

However, the value of this comparison is limited by the lack of information on cancer stage for most cases, which inhibited evaluation of survival by stage. A majority of patients with lung, stomach, colorectal, and breast carcinoma began MDB after a more or less documented failure of surgery and chemotherapy, i.e., in a very advanced stage. It is possible that cancer patients who recovered after treatment never sought MDB, but those with short or very short survival also tended to be excluded from Di Bella therapy. In fact, there was a 1-year mean time lag between the date of disease incidence and the first MDB date. To avoid this bias partially, each index patient was matched with subjects alive at the date of the first MDB therapy. The reverse bias (exclusion of recovered patients) could not be avoided. This limitation may at least partially explain the worse result with MDB than without MDB. However, patients with short survival were not totally excluded from the comparison group, as shown by short term survival probability.

A detailed analysis of the 27 long term survivors failed to identify a significant number of successes attributable to MDB. Only in 2, or perhaps 3, cases did other therapies fail to justify the result. These were one leukemia case in a youth, one stomach cancer case, and perhaps one advanced colorectal carcinoma case. This small number is compatible with the proportion of patients with a very severe prognosis who survived more than 10 years in population-based series. These cases are explained by diagnostic errors or by the occurrence of sporadic, slowly growing neoplasms.15 None of these patients were treated with somatostatin.

In conclusion, results from this study do not support any evidence of the efficacy of the anticancer strategy proposed by Dr. Di Bella in terms of the survival of this historical series of cancer patients. This result should be considered conclusive as far as the
cases examined are concerned. These, however, represent a large, nonbiased sample of the whole Di Bella therapeutic experience. Historical survival studies tend to be biased toward better results in comparison with clinical trials, due to selection of cases with more favorable follow-up. Apparently, this was not the case in the MDB series. Survival of children with leukemia was particularly low. Currently, it is impossible to determine whether this was due to a selection of unfavorable cases or a diversion of some subjects from effective therapy.

REFERENCES