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Alternative therapies and the *Di Bella affair* in pediatrics. A questionnaire submitted to Italian pediatric oncologists and hematologists

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Abstract

***Background and Objectives*. Over the last 2-3 years in particular, the so-called *Di Bella therapy* (DBT) become the most famous of alternative treatments applied to pediatric oncology and hematology in Italy. Many Italian oncologists and hematologists had to cope with the problems that it introduced and the treatment also elicited heated reactions all over Europe. We attempted to evaluate the impact of this treatment on children with cancer.**

***Design and Methods.* A questionnaire prepared with the aim of addressing the use of alternative therapies in pediatric hematology and oncology was circulated to the 48 centers (or divisions) belonging to AIEOP (*Associazione Italiana di Oncoematologia Pediatrica) [Italian Pediatric Oncology and Hematology Association*] and FONOP (*Forza Operativa Nazionale di Oncologia Pediatrica) [National Pediatric Oncology Task Force*]. The questionnaire consisted of 9 questions elaborated to give credit to the case-related and professional experiences of the colleagues we contacted.**

***Results.* Forty-three centers replied to the questionnaire. Request to switch to DBT represented a considerable problem, involving the vast majority of centers participating into this study; however, case quantification varied greatly from center to center. One of the most significant aspects is that children *switched* to DBT, abandoning conventional therapies, were often relapsing or had had multiple relapses (from solid tumor or leukemia), but some children abandoned conventional therapies at an early stage and*/*or without fully exploiting the curative potential of these therapies.**

***Interpretation and Conclusions.* This study allowed us to obtain an evaluation of the impact of DBT in children with oncologic or hematologic disorders. It also highlights the importance of cultivating physician-parent dialogue and provides an opportunity for a few pedagogic thoughts on the attitude and opinions of pediatricians on this problem.**
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Key words: alternative therapies, bioethics, childhood neoplasia, leukemia, Di Bella therapy

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For a long time, oncologic diseases have been a fertile field for elective application of *alternative therapies* in both adults and children. According to the latest literature, this situation has not changed in the last 5-6 years in Europe, North America or Australia. Standard, conventional and statistically effective treatments do not always provide a definitive solution for an individual person with one of these diseases; the treatments are also burdened by severe side effects. This is one of the key factors that shapes the psychological environment for all use of alternative therapies.[1-9]

However, in adults as well as in children, therapeutic methods of unproven effectiveness in particular and alternative therapies in general are applied, at least in most situations, *in addition* to standard therapies (or together with these proven and approved therapies), whose continuation is not affected and is indeed recommended by physicians. There is a considerable body of qualified literature which stresses that physicians must not refrain from providing unbiased comment on alternative treatments, which in any case must never interfere with orthodox therapies.[3-13]

In some situations,[14,15] however, as exemplified by the so-called *Di Bella treatment* (DBT) in Italy, an alternative therapy is proposed as *a replacement* of the conventional one. In addition to the severe intrinsic damage entailed by the very act of replacement, such alternative therapies can have a serious effect on the relationship between the physician and the patient (and/or his parents), placing a strain on an approach based on dialogue and communication and undermining the trust that is the key factor of this approach. Both the physician and the patient are motivated to seek the *best treatment*; the physician finds it, with rare exceptions in cases of terminal patients,[2,3,16] in the standard or evidence-based therapy, whilst the patient, who may be experiencing a crisis or a period of mistrust, often hopes to find the best treatment among unproven therapies.

The *Di Bella affair*, which essentially involved an alternative therapy for oncological and hematologic diseases was initially a strictly Italian *cause célèbre*, but has aroused considerable interest outside Italy as well. After a few years of inconspicuous use, the treatment regularly made headline news from the second half of 1997 to the first half of 1999 and interest in it has still not apparently come to an end.

Pediatrics, and more specifically pediatric oncology and hematology, was not one of its elective fields, although certain *pediatric cases* attracted considerable attention and stirred public opinion, with massive coverage in the press and other media. In any case, the entire episode was handled in the qualified international medical literature[17-30] without mentioning any pediatric aspects. Italian medical literature[31-34] followed suit, except for a few opinions expressed in pediatric periodicals.[35,36]

We wondered whether this silence of pediatricians in the medical literature was actually justified in some way, perhaps by the limited number of pediatric patients with cancer *switched* from conventional treatments to the Di Bella therapy. We thought that the question could be settled by submitting a questionnaire to pediatricians who cared for children and adolescents with cancer in particular in the two-year period mentioned above.

We sent a questionnaire to 48 pediatric oncologic or hematologic centers (including a few pediatric Divisions active in cancer treatment), which were members of AIEOP (*Associazione Italiana Ematologia Oncologia Pediatrica) [Italian Pediatric Oncology and Hematology Association*] and FONOP (*Forza Operativa Nazionale di Oncologia Pediatrica) [National Pediatric Oncology Task Force*]. Forty-three of the centers returned the completed questionnaire; the other 5 politely declined. The questionnaire addressed the use of alternative therapies in pediatric hematology and oncology and sought to give pediatricians involved in field work the opportunity to report their experience (to the extent they deemed most appropriate). The core issue of the questionnaire was, against the problematic backdrop of alternative therapies in general, to find an orientative approach to quantifying the cases of children *switched* to the Di Bella therapy.

The pages that follow present the questionnaire, followed by a summary of the answers and remarks and our concluding comments.

The questionnaire

We did not write the following questionnaire with the aim of obtaining indications in absolute terms. Rather, our goal was, on the one hand to give credit to the case-related and professional experience of the colleagues we contacted and, on the other hand to allow them to come out of the loneliness and silence in which many of them had had to handle the situation. Briefly, the problematic impact that certain *pediatric cases* had on the nation and on many pediatric oncologists and hematologists prompted us to gather these latter's personal experiences. Accordingly, we felt it inappropriate to include any questions regarding case quantification per year (i.e. cases/year received in the individual centers). This parameter would have allowed us to perform a quantitative evaluation, center by center, of the extent of the various issues covered by the questionnaire; but on the other hand it would have also introduced a criterion for evaluating the work of the various centers which had nothing to do with the spirit of our enquiry. However, we did make provisions (see question #5) so that any center wishing to do so, as indeed was often the case, could provide us with case and percentage data which could be taken into account.

Here are the 9 questions of the questionnaire, which would seem to require no comment in view of their inherent simplicity.

1) Were you asked to treat children with cancer or leukemia whose parents proposed alternative therapies such as homeopathic treatments, esoteric practices, abstention from transfusion (Jehovah's Witnesses), others (see later on)?
   yes ☐ no ☐

   If your answer is "yes", would you please provide details: for example, how often did you encounter this problem during the last 10 years? And in particular, was it necessary to resort to the Juvenile Court?

2) Did you assist children who had already been treated with the "Di Bella therapy" before being referred to you?
   yes ☐ no ☐

   If the answer is "yes", how many children included this "phase" in their anamnesis?
   For which disorders?
   What was their condition when they contacted you for treatment?
   Follow-up information and current condition.

3) Were you asked to *switch* to the "Di Bella therapy" for any of the children with neoplasia treated in your Centre?
   yes ☐ no ☐

4) If the answer is "yes":
   — For how many children was this request made?
   — By which disorders were they affected?

5) Unless you were involved to a very limited extent and/or sporadically, can/would you provide a further quantitative estimate for question #4? E.g. as a percentage with respect to "new cases/year" brought to you for treatment?

6) When (as we can assume) you tried to resist this request, were you able to have it cancelled?
   — if so, for how many children did you succeed?
   — and for how many did you fail?

7) Did you have to resort to the Juvenile Court or to other public authorities in the attempt to avoid the "switch"?
   yes ☐ no ☐

8) Did these requests to *switch* to the Di Bella therapy lead to any unease or distress (difficulty in dialogue)
   a) with other patients in the ward and with their parents? yes ☐ no ☐
   b) among medical staff? yes ☐ no ☐
   c) among nursing staff as a whole? yes ☐ no ☐
   d) with volunteers' associations or parents' associations yes ☐ no ☐
   (Would you like to comment?)

9) Did you have the opportunity to follow the evolution of the disease in children *switched* to the Di Bella treatment? (any reply or follow-up comment would be particularly appreciated)

   Please note that any further comment or additional remark you would like to include will be extremely welcome.

Summary of answers and remarks

The answers yielded the following results through numbers and/or comments:

Question #1 (quantitative orientation of the request for alternative therapies in a period which we chose to limit to the last ten years)

Positive answers: 30 (Negative answers 10 or no answer 3).

Case quantification (on positive answers) varied greatly from center to center: the minimum was 1-2 cases and the maximum was 50 (and specified *during the last 10 years; < 10 cases in the previous 2 decades*). We received this answer from an important oncologic center in Lombardy, but requests in general for alternative treatments amounted to 10-20 cases in the 10-year period for Veneto, Latium, Liguria and Apulia. Requests for homeopathic treatment were prevalent (one center in Emilia reported 20-30 requests in the decade, in addition to "official" treatment), but a few esoteric therapies were also requested. Although our choice was perhaps not fully justified, we included refusal of transfusions (Jehovah's Witnesses) in this question, and the problem turned out to be significant. Nineteen centers had had to deal with it, often requesting the intervention of the Juvenile Court (orientative indication: for at least 30 children). In particular, one center in Lombardy which conducts prominent hematologic work resorted to the Juvenile Court 10 times in the ten-year period.

Question #2 ("Di Bella therapy" before the child was entrusted to the center).
We received 12 positive answers.

The number of these patients was modest (20 in all) and their diseases were acute lymphoblastic leukemia (ALL) (5); non-Hodgkin's lymphoma (NHL) (2); neuroblastoma (2); retinoblastoma (2); osteosarcoma (2); medulloblastoma (1), Ewing's sarcoma (1), low-grade glioma (1), peripheral neuro-ectodermal tumour (PNET) (1), germ-cell tumor (1), urologic tumor (?) (1) and brain tumor (1).

The recovery of these patients, who subsequently switched to conventional therapies, was very limited.

Question #3 (switching from conventional/standard therapy to the Di Bella treatment)

This question yielded the highest number of *positive answers* (34 centers); *negative answers* were given by 9 centers. Only a very partial correlation between the size of the problem (number of cases *switched* to the alternative therapy) and the treatment capacity of the center was detectable from the answers: not all the centers that had the largest numbers of patients reported the highest numbers of requests to switch. Two neuro-surgery centers were among those which declined to answer.

Question #4 (dependent on a positive answer to question #3)

It seems interesting to give a *diagnosis-dependent* quantitative estimate of the cases *switched*, even temporarily (see question #9), to the Di Bella treatment. Estimated conservatively (some questionnaires said "many times") this yields a total of 143 children; we were given a diagnosis for 131 patients; for 6, the answers merely indicated "terminal phase"; 6 others were not specified (nor did we feel it useful to ask for details). The following diseases (and cases) were reported to us: central nervous system tumors (24 children), neuroblastoma (12 children), NHL (9 children), osteosarcoma (8 children), Ewing's sarcoma (8 children), rhabdomyosarcoma (4 children), medulloblastoma (3 children), Wilms' tumor (3 children), soft-tissue sarcoma (3 children, including one with alveolar sarcoma), Hodgkin's disease (HD, 2 children), PNET (2), adrenal gland carcinoma (2), and single cases of each of the following tumors: sellar astrocytoma, retinoblastoma, hepatoblastoma, rinopharyngeal carcinoma, germ-cell tumor, ependymoma, fibrosarcoma, glioma, glioblastoma. There were 36 cases of ALL, 5 of acute myelogenous leukemia (AML) and 1 of Philadelphia-positive chronic myelogenous leukemia. However, we feel that these diagnoses and case reports deserve more comment. For at least 1/3 of the children, the answers specify that the patients had a long history of disease and treatment (often with multiple relapses during the time from diagnosis) or had reached the terminal phase when the *switch* was requested. This provides a sensible reason for the choice of a significant number of health workers (and centers) to share with the parents the feeling that the "switch" was acceptable (as detailed later). On the other hand, the answers show that 11 children undergoing conventional therapy interrupted their treatment (some even precociously) to switch to DBT. In particular, as regards solid tumors, in 2 relapsing cases of osteosarcoma (out of the total of 46 cases) *valid salvage therapies* were refused (the children died). Furthermore, patients with the following diseases were deprived of conventional therapies from the outset: 1 rhinopharyngeal carcinoma, 1 esthesioneuroblastoma (both lost from follow-up) and 1 adrenal gland carcinoma (deceased); one child with PNET, who *switched* to DBT despite achieving complete response after a second relapse, also died. As regards leukemias, 3 children with ALL were not transplanted: one after first relapse having a compatible related donor, one after a third complete remission with an already-identified unrelated cord blood unit available, and one in fourth hematologic remission of the disease with an identified unrelated bone marrow donor. Moreover, validated therapy was interrupted in order to switch to DBT in one child with ALL during administration of the initial protocol (lost from follow-up) and in 1 child who was actually already in remission but died only 4 months after the *switch*.

Question #5 (further quantitative detail on switches, provided by centers which gave positive indications and case details for questions #3 and 4)

Sporadic involvement was reported by 8 centers. Four other centers reported percentages of < 1% (related to case numbers), but there were also much higher estimates: approximately 3% (5 centers): 5-10% (6 centers). However, approximately one half of the centers we contacted did not answer this question.

Question #6 (attempts to dissuade from the switch to Di Bella therapy)

The answers showed in summary a negative outcome (the *switch* was carried out) for 63 patients and a positive outcome (conventional therapy was continued, renouncing the *switch*) for 35 patients. Six centers reported that they did not resist switching to the DBT because conventional therapy offered no favorable or reliable prospects (as detailed later).

Question #7 (resorting to the Juvenile Court)

Only 5 centers gave a positive answer to this question. The most saddening episode concerns 2 *initial* cases of ALL. The other 3 positive answers provided no case details. The frequency of the intervention of the Juvenile Court was in any case found to be much lower than that for Jehovah's Witnesses (question #1).

Question #8 (unease in the ward)

The answers were particularly wide-ranging in relation to the various options proposed (a-d). In summary, positive answers (distress in dialogue) to one or more options were given only 19 times. In greater detail, 14 positive answers were given to option (a), 9 to option (b), 6 to option (c) and 3 to option (d). These answers were in fact very often positive for multiple options (a+b+c or b+c).

Question #9 (follow-up of patients switched to the Di Bella therapy).

No answer was given in 8 questionnaires; 5 simply answered *No* (no follow-up experience). Other exhaustive and usable answers yielded a prevalence of *death* (for 51 patients) or *progression of the disease* (18). There were also 9 answers reporting *lost from follow-up*. Seventeen other patients were reported to have "returned" to conventional therapy.

There were also 8 unusual answers of uncertain interpretation. One concerned a diagnostic uncertainty (severe *pulmonary stasis* due to myocardiopathy arising from prior conventional therapy with anthracyclines or metastatic osteosarcoma *replacement lesions* in the lungs); the child was cured after a heart transplant, before which she had undergone the Di Bella therapy. The success of one case of NHL *switched* to DBT was attributed to complete remission achieved by prior conventional chemotherapy. Three *disease-free* cases following DBT (1 NHL, 1 ALL in a patient with Down's syndrome and 1 M7 AML) had already been treated earlier by, respectively, the induction treatment of the NHL 91 protocol (completed), consolidation therapy of the ALL AIEOP 9501 protocol (also completed), a cycle of induction of the AML AIEOP protocol (however, this patient was lost early in follow-up). One patient with HD was judged to be partly responding after 7 months of DBT and in another case the disease was undergoing *slow and modest regression*. A patient with a sellar astrocytoma, partially removed surgically, receiving DBT was asymptomatic.

Concluding comments

First of all, we would like to consider some of the key aspects of the questionnaire (questions #4 and 5). As regards the type of patients involved (question #4), the children *switched* to the Di Bella therapy were often relapsing (or had had multiple relapses). This (i.e. a *switch* which was not precocious with respect to prior standard therapies) was reported for at least 1/3 of the total of 143 *switched* cases. On the other hand, 11 children (5 of whom had leukemia) abandoned standard treatments at an early stage and/or without fully exploiting the potential of these treatments. This is certainly the most saddening aspect of the *affair*, often dramatically involving pediatricians as well as magistrates, the press and the public opinion.

Answers on the *percentage* (in a two-year period) of requests to *switch* (question 5) varied widely from *sporadic* (8 centers), to < 1% (4 centers), to ~ 3% (5 centers) to 5-10% (6 centers). Moreover, this question was responded to by a small number of centers (23 out of 43), which were also heterogeneous. This prompts further thought on the importance of nurturing the best possible relationship between the physician and the patient (or the medical team and the child's relatives),[37] since this relationship is fundamental for compliance with standard treatments and as such prevents all temptation to *switch* to other (alternative) treatments.

Concerning alternative treatments in general, North American literature[6] in particular stresses the need to cultivate the physician-parent dialogue by modulating it according to the cultural level of the parents. It is therefore evident how important it is for medical schools to prepare students to handle this fundamental aspect of treatment competently, without leaving it purely to the sensitivity, intelligence and individual culture of the future physician to devise and develop communication and information strategies to meet the requests, demands, anxieties and fears of patients and/or their relatives.

As reported in American literature the approach to switching to unproven treatments for terminally ill children can be reasonably justified and can be judged to be fully ethical.[38,39] In fact, it is evident that in these patients alternative therapies can meet the parental need to perform treatments aimed at contrasting imminent negative outcomes of oncologic diseases against which official medicine can only offer palliatives. Rekindling or sustaining illusory hopes of recovery can even have a psychosocial comforting role in accepting or handling death. On the other hand it is obvious how alternative therapies (of unproven efficacy) have a dramatically and sadly different role in patients who despite relapsing still have objective chances of recovery and cure. It is sufficient to consider, in this regard, the results of patients with relapsed leukemia,[40-43] patients with relapsing neuroblastoma[44,45] or with Wilms' tumor,[46] to grasp immediately the extent to which unconventional treatments precluded the possibility of cure. The application of alternative treatments to recently diagnosed patients or to patients fully responding to proven and evidence-based therapies, i.e., to therapies whose effectiveness has been validated by studies which can be replicated by the pediatric oncologic and hematologic community, stands out even more as a tragic denial of the *right/duty* to treatment.

To conclude, as regards alternative therapies it would be paradoxical to accept the price of suffering and/or of human lives entailed by avoidable failures. If, as the saying goes, successes gratify but failures teach, the basic lesson for everyone is that any possible failure must be view critically as soon as it appears on the horizon. Sensitivity and attention to this aspect should be part of the culture of every physician; indeed, it should permeate his awareness and his professional behavior. It should also permeate the work of medical scientific societies and institutions which have the ethical mandate to produce information and produce it in a clearly comprehensible form, indicating scientifically grounded choices and behaviors.

We found that our pediatric oncohematologic colleagues welcomed the opportunity to state their viewpoint (by answering our questionnaire) on the impact of the *Di Bella affair* on their professional experience. Indeed, the almost unanimous response to the questionnaire from the colleagues we contacted confirms that circulating it was a worthwhile endeavor.

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