Abstract
The history of treatment of childhood leukemia is a meaningful model of ethical, bioethical and organizational repercussions of medical progress. Specifically, it has provided precious indications and very useful tools to cope with several of the more important problems of modern medicine: the value of controlled randomized studies; the risks of intense medicalization impairing the quality of care; the importance of a valid doctor-patient relationship; the psycho-emotive involvement of the pediatric staff; and last but not least, the need of an unrelenting effort of humanization of the procedures and environments, hand in hand with the frequent adjustments of the protocols according to scientific and technological progress. Finally, the authors comment upon the first cures (1962-1966) observed in the Pediatrics Clinic of the Sapienza University of Rome.

INTRODUCTION
The treatment of childhood leukemia is not only a fascinating chapter of the history of medicine, but also a meaningful model of ethical, bioethical and organizational repercussions of medical progress [1]. The cure in about 80% of cases of a disease considered inevitably fatal until the early 1960’s is the result of an enormous effort in clinical experimentation studies without precedents in the history of medicine; an effort which has required the involvement and dedication of many thousands of scientists, clinicians, children and their families, mainly in the USA and in Europe. This unique experience, initiated in the late 1950’s, has provided precious indications and very useful tools to cope with several of the more important problems of modern medicine: the value of controlled randomized studies; the risks of intense medicalization impairing the quality of care; the need to adapt doctor-patient relationships to changing circumstances; the problems of impending death and of therapeutic obstinacy. A further important feature of this evolution has been the need of a continuous organizational activity aimed at adapting structures and personnel to the requirements of humanization of the procedures and environments, in addition to the changes imposed by scientific and technological progress. These numerous and delicate problems created by the hectic cadence of clinical and prognostic changes caused by technological progress have now become one of the main preoccupations of modern medicine. However, while technological progress runs autonomously on the basis of new additions to the know and know-how in the various areas, coping with the essential spiritual and emotional needs of patients often lags behind or is more or less completely neglected in the current clinical practice. Therefore, it seems useful to go again along the path of this pioneer experience, and to examine the problems encountered in successive steps.

HISTORICAL OUTLINE
The first complete clinical and hematologic remissions, still of brief duration, of childhood leukemia were obtained by S. Farber et al., 1948, [2] with the use of amopterpine. The use of corticosteroids [3-7] and of 6-mercaptopurine [8-11] improved the quality and duration of these remissions, but did not change the inevitably fatal outcome of the disease. In the 1950’s and 1960’s, systematic, large-scale, control-led and randomized clinical trials with associations of chemo therapeutic drugs were conducted in the USA by the Leukemia Group B [12-20] and the Children Cancer Study Group A [21] and in Europe by J. Bernard et al. [22-24], G. Mathé et al. [25]. They led to the elaboration of shared protocols that allowed a progressive and consistent increase of the remissions: at that point part of the patients became the so-called long-survivors. At that time no one ventured to pronounce the word “cure”, which was clearly in contradiction of modern medicine.
with the intrinsic lethal meaning of the term “leukemia”. Nevertheless, between doubts and hopes, in the mid-1960’s the term “cure” started to appear in the literature: J. Bernard and M. Bessis, 1965: “Peut-on guérir les leucémies?” [24]; WH Nyhan, 1966, “Editorial comment: more on the treatment of acute leukemia” [26]. In reality, the prolonged observation in the following years showed that many long-term survivors after the termination of maintenance therapies were authentic cures. The impossible thus became a splendid reality: WW Zuelzer and G. Flatz, 1960, [27] first observed that some features inherent to the patient and to the early manifestations of the disease influenced the response to therapies, the course and the final outcome. In particular, he showed the prognostic relevance of the presence or absence of leukemic hyperleucocytosis, of involvement of extramedullary sites and of age. These observations and the subsequent identification of numerous hematologic, immunologic, and genetic factors with prognostic significance allowed the experimentation of differentiated therapeutic protocols on homogeneous groups of patients, which resulted in a considerable increase in the proportion of cures. Further progresses were obtained with the introduction of vincristine [28, 29] in the initial treatment and in the so called “re-induction”. The introduction by the researchers of St Jude Children’s Research Hospital in Memphis [30, 31] of the prophylaxis of central nervous system (CNS) relapses within a protocol of “total therapy” led to a further meaningful increase in the number of “long-survivors” and of cures in the early 1970’s. In Europe, protocols of radical therapy were introduced by Riehm [32, 33]; and at the turn of the century the total cure rate had gone up to about 80%.

In December 1973 the Gruppo Italiano di Ematologia Pediatrica (GIEP) [34] was constituted in Rome in order to promote research on childhood leukemia and its treatment, as well as the diffusion of shared treatment protocols [34-40]. In 1980 the Italian Register of “off therapy” patients was instituted [41].

In the Pediatrics Clinic of the Sapienza University of Rome the first cures were observed in five out of 99 children (5.5%) enrolled in the period 1962-1966 (follow up on 31 December 1993) and treated according to different protocols, all including the use of vincristine sulphate [42-44]. A remarkable case was that of a 5 year-old child with a acute lymphoblastic leukemia (LLA) diagnosed in August 1962, who underwent a complete clinical and hematologic remission after treatment with cortisone, 6-mercaptopurine and methotrexate. She relapsed twice in 1963 and her conditions were very poor at the end of this year. A new remission was obtained in January 1964 with vincristine associated to cortisone; but in February 1964 this treatment had to be suspended because of a very severe neurological syndrome. The patient did not receive any further antiblastic treatment, was regularly controlled in the following years, and did not relapse [44]. She was in good health at the last follow-up at the end of 1993.

DISCUSSION

The cure of childhood leukemia has a high human cost for the child and his family, because of the intense medicalization in the therapeutic process. At the same time, due to early diagnosis and therapeutic intervention, the child will never experience on his or her way to cure the tremendous symptoms and evolution of the natural disease, but only modest and transient symptoms which are promptly removed by early therapeutic intervention.

The “true disease” of the cured child will be the continuous and invasive manipulations; the devastating, although generally reversible, collateral effects of the powerful antiblastic drugs; the death anguish that surrounds and will accompany him or her throughout and after the treatment. In fact, despite the high rate of cures, the uncertainty of the prognosis in the individual patient is a source of great disturbance for everyone – patient, family and carer team [45-47]. The awareness of such an existential, pervasive condition and of the behaviours it can trigger is an essential component of a project of global care.

An important implication of the technological and therapeutic progress which has come under the spotlights with the treatment of child leukemia has been an expansion of the physician’s tasks and a profound change of his role. First of all there is the emergence of new heavy responsibilities, as a consequence of the need to be involved in dramatic decision choices and to accept a closer communication with the sufferer and his or her family. Such an increasing awareness of the changes in the relations with the patient and his or her family has eventually sanctioned the crisis of the paternalistic model of physician-patient relationships, as well as the end of the proxy to the physician in the management of patients’ lives. Moreover, the need of a continuous adaptation of sanitary structures to technological progress and to the aforementioned requirements of humanization has made it necessary to change the role of the clinician to clinician-manager or, tout court, to manager, which created several significant problems often not yet resolved - in fact, not always the best clinicians are also the best managers, and vice-versa.

In the early phases of the history of the treatment of childhood leukemia the main tasks were to design ad hoc structures suitable to ensure a good life quality for the child and to promote the presence of parents, other family members and friends, besides the creation of structures for short or very short hospitalizations (“day hospital”) and for intensive therapy, sterile rooms, temporary housing facilities for the families, etc. [48, 49].

The intense emotional involvement, the conflict between feelings of omnipotence and feelings of guilt and frustration, when the results do not correspond to the expectations, tend to shape a genuine “parallel disease” of the health operator. Several subconscious forces are a cause of suffering in the staff of onco-hematologic departments: a-priori prejudices; reluctance of carers to be involved in interpersonal relationships with patients and families who experience deep physical and psychological suffering; interference by prior personal experiences and dynamics with sickness and death of loved ones;
and last but not least, the frequent tendency of staff members, including psychologists, to identify themselves with the protagonists of the painful disease experience. The consequences are poor communication between staff members and between them and patients and families, absenteeism, burn-out, and a high rate of turnover. These processes occur in every situation in which severely ill patients require aggressive interventions; but the efforts to recognize the subconscious factors so far mentioned and to cope with their adverse consequences can help creating a more collaborative and satisfactory climate for all those involved in the disease - carer team members, patients and their families [50].

The change of prognostic and clinical paradigms, the consequent changes in structures and organizational patterns, the intense medicalization, the great emotional involvement of the carers require a continuous rethinking of the carer’s work style, aimed at minimizing negative reactions (guilt, frustration) and facilitating positive empathic attitudes vis-a-vis the painful condition of patients and families. Medical-technical interventions should be increasingly implemented in a context of convergence of the attitudes and behaviours of the teams responsible for the different parts of such interventions. This makes that physicians and other carers need to perform equally well two quite different professional tasks: namely, 1) optimal management of the disease by rational progress through the separate steps - hypothesizing on the basis of symptoms and signs, choosing the more appropriate clinical tests, diagnosing, treating; and at the same time 2) the integration of technical interventions in a broader context of taking care of the patient.

Milani Comparetti [51] warns about the difficulties of such an integration between different tasks. In fact, the individual caretaker’s attention is often not ipso facto so comprehensive as to allow him or her to make coherent choices, resulting in alternative pathways being followed by “jumping” from one level to a different one. The solution is to progressively reconcile what is originally separated by the perspectives from different points of view, aiming at optimal coherence and strategic coordination - a result which is best obtained by the confrontations in multidisciplinary work.

In our experience the integration of psychological support in the work of pediatric onco-hematologic teams allowed the activation of communication circuits and facilitated the sharing of emotions within the staff and between staff, patients and families. This made it possible to overcome the traditional paternalistic approach in the physician-patient relationship and to build an authentic therapeutic alliance.

CONCLUSIONS

The history of the treatment of childhood leukemia constitutes a highly meaningful model of the complex problems produced by scientific and technological progress and of their ethical, bioethical and organizational implications in medicine. The increasingly prevalent role of advanced technological tools goes hand in hand with an increased risk of negative consequences of their inappropriate use on the essential humanitarian components medical care – a risk that becomes more and more evident with the rapid increase of aggressive high-tech interventions in hitherto incurable patients.

In foreground are the problems of communication, particularly as concerns changes in the physician-patient relationship which require a more thorough understanding of the type, the levels and the depth of involvement not only of the patient and his family, but also of the members of the carer team. The integration of psychological support in the operations of carer teams appears to be an important step in the achievement of the desirable goals.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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