The importance of "early diagnosis" to improve the prognosis in children with cancer: a prevalent concept for 50 years with little scientific support

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Abstract

Cancer mortality in Mexican children has not decreased to the levels reported in developed countries. A commonly proposed explanation is the high percentage (53.7%) of patients diagnosed at advanced stages (III/IV), which is attributed to erroneous assumptions or mistakes in the diagnostic approach –a questionable consideration taking into account that both time to diagnosis and the proportion of advanced stage cases in Mexico are similar to those in developed countries. In most cancer cases in children, the number of days elapsed from the moment of the first symptom to the cancer diagnosis is not correlated with clinical stage, and neither with the probability of survival. Survival success largely depends on comprehensive treatment (specific and for the care of complications). This view calls for strategies mainly aimed at spending more resources on efficacious and efficient therapeutic strategies, comprehensive oncology training of healthcare personnel (physicians, nurses and technicians), diagnostic technologies, promotion of interinstitutional and international collaboration and socioeconomic support to families during the therapeutic process.

KEY WORDS: *Cancer in children. Time to diagnosis. Cancer stage. Cancer survival.*

Introduction

In 1965, Dr. Alejandro Aguirre, head of the Department of Tumors at *Hospital Infantil de Mexico*, wrote "Malignant diseases of childhood. Early detection"; in this article, he reviewed the main malignant tumors in children that had been treated in a five-year period (1951-1955). He concluded his analysis with the following:[1]

> We want to conclude by calling on pediatricians, who form the advance party in the fight for children's health, to join us in this crusade against childhood cancer. In this crusade for early detection of the disease, which is a universal characteristic sign of this era of medicine, by developing this anticancer mentality, of continuous alertness against these ailments, and we might say with a prophylactic attitude, discovering these neoplasms at their early stage of localization so that appropriate surgery, radiation, and perhaps chemotherapy, can prevent their metastatic spread, which is necessarily fatal.

Fifty-two years have elapsed and the same problem continues: 57.3 % of children treated for cancer (solid tumors) in Mexico are diagnosed at advanced stages (stages III/IV).[2] What have we done or left to do that after so much time this problem persists? We do not know, but it is a fact that this has justified the establishment of campaigns aimed at detecting or diagnosing at early stages in children with cancer, aimed at the general population, primary care or family doctors and pediatricians,[3] even when there is no scientific evidence of their success.

In this narrative review, we will analyze the situation of cancer mortality in children, the peculiarities of

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cancer diagnosis in this population, the studies that address the problem based on time to diagnosis (TTD), the difference between TTD, diagnosis at early stages (localized disease) and opportune diagnosis (prognosis) and, finally, the implications of these concepts in possible strategies to achieve survival with quality of life in these children.

Cancer mortality in children and their comprehensive treatment

The assessment of cancer mortality in the population, both in children and adults, when no other instruments are available, is a good indicator of the efficacy of a comprehensive treatment.[4,5] Pediatric cancer mortality in Mexico is known to have not decreased at the same rate as in developed countries.[5] Currently, 57 children under 15 die annually per million of Mexican children, in contrast with 22 to 30 in developed countries.[5-7] Although there is no certainty on the reason for this difference, two non-incompatible assertions have been disseminated:

- The need to increase specific diagnostic-therapeutic oncological resources, together with those required to prevent, mitigate or treat associated complications.[5,6]
- The delay in oncological medical care owing to late diagnosis.[1,8]

As previously mentioned, this last assertion has motivated the implementation of educational strategies, aimed both at the general population and health personnel.[3]

Incidence of cancer in children

Little has been reported about the incidence of cancer in Mexican children. Available data have been mainly reported by the Mexican Institute of Social Security and originate in Mexico City, State of Mexico, Morelos, Guerrero and Chiapas. Of this registry, an incidence of 128 annual cases × 1 000 000 < 15-year old subjects has been estimated, a figure slightly lower than 140 estimated worldwide.[9] In addition, this incidence has remained stable from 2001 to 2013.[5] Specifically, approximately 46.2 % of new cases are expected to correspond to leukemia, 12.1 % to nervous system tumors, 10.7 % to lymphomas and the rest to other solid tumors.[5] With these data, it has been estimated that a pediatrician with an average of 5 appointments per day (≈ 1200 in one year) would see a cancer patient every 6 years.[10] In England, Feltbower et al. estimated that a primary care doctor would provide care to one or two children with cancer in 20 years.[11] Hence, it should be admitted that cancer in children is rare and, in general, unlikely to be a common cause of children's medical care. Frequently, cancer is suspected in a child as a consequence of a differential diagnosis for any other more common disease. Finally, it has been estimated that approximately 25 % of childhood cancers will be diagnosed at an emergency department, without previous examination in a doctor's office.[10]

Childhood cancer symptomatology

Symptom diversity of pediatric in cancers has been widely reported,[10-12] which can resemble any pathology, and although there are some signs and symptoms inherent to some neoplasms (e.g., leukocoria in retinoblastoma), most have low specificity and, therefore, the proposed guidelines only direct to suspicion.[10,13-16] A considerable proportion of clinical symptoms variability of depends on tumor site, its size and association with involved organ(s) functionality. This way, large or accessible tumors to physical examination are usually more easily detected. If they affect organ function, they will also generate more symptoms and, therefore, greater demand for care. However, it is highly common for some tumors to manifest with non-specific symptoms, such as mood or behavioral changes,[17-19] situations that are difficult to initially be attributed to a neoplastic disease.

In addition to the above, age can both limit and facilitate diagnosis, since very young children compared to older ones show a smaller repertoire of signs. Given this non-specificity of clinical symptomatology and its high variability, a proposed premise to suspect pediatric cancer is that any patient with one or more persistent or progressive symptoms should raise cancer suspicion;[15,20] uncertainty can translate into an erroneous opinion; even in developed countries, 52 % of pediatric patients with cancer had an incorrect initial diagnosis at first assessment.[13,21]

Definition of time to diagnosis

TTD has been defined as the elapsed period since cancer-associated symptoms initiation until its diagnostic confirmation, either histopathological or by other incontrovertible evidence (bone marrow cytomorphological study in children with leukemia).[16,22,23]

For analytic purposes and for its implications in strategic actions for diagnosis, TTD has been divided into two periods: one dependent on the patient (relatives) and another on the health system (doctor). The former encompasses the days elapsed since the moment the patient or his/her relative detect a cancer-associated symptom until the first medical consultation. The second includes the days since that contact until diagnostic confirmation.[16,22,24]

Some authors have found that variability of the first period is influenced by the minor's age, parents' education and the type of tumor,[24] although others have not identified this association.[25] In some studies, TTD has been similar, with medians ranging from 2 and 12.8 weeks;[22] at *Centro Médico Nacional Siglo XX* Pediatric Hospital, it has been 4 weeks, similar to that reported in developed countries; in Colombian patients with acute leukemia, this period was shorter when the parents detected a more notorious symptom, such as skin bleeding, in comparison with pallor (14 versus 40 days).[26]

For the second period, two aspects have been considered fundamental in their duration:

- The level of suspicion by the doctor or doctors about the possibility of a neoplasm.
- Availability or not of useful methods to confirm the diagnosis.[27-29]

The period attributed to doctors is of less days in developed countries; however, the effect of the lack of medical acumen or of the necessary resources for diagnosis is not analyzed.[29,30]

Some analyses have included the reference time from first contact clinics to oncological care centers as an involved factor.[25,31] More swiftness (< 5 days) has been observed in better integrated health systems,[27] as opposed to those with administrative deficiencies.[27,31]

About TTD in Mexico, at least in lymphomas, it has been established to be 20 weeks,[24] as compared to 7.1 to 14 weeks in the United States;[22,23] in particular, for Burkitt lymphomas, TTD was less than 4.5 weeks at *Centro Médico Nacional* Pediatrics Hospital,[32] with 80 % of patients being at stages III-IV. According to the results of the few studies that have been carried out, it can be concluded that TTD in children with cancer in Mexico is not very different from that determined in the world.

Correlation between time to diagnosis, oncological stage and biological behavior of the neoplasm

In the minds of all doctors is to establish a diagnosis as soon as possible for the opportunity of finding a tumor at early stages or, in other words, localized (I or II). In this sense, and although not consciously, the doctor considers there is a positive correlation between time to diagnosis and clinical stage: the longer the time to establish the oncological diagnosis, the more advanced the tumor stage at the moment of care.

It is evident that a patient with a localized tumor that is 100 % resectable has higher chances of cure; in addition, early stages are associated with higher survival;[33] however, only in few tumors has positive correlation between TTD and clinical stage been found. In a study carried out by our group, positive correlation was only found in patients with retinoblastomas and Hodgkin's lymphomas, which is consistent with records in the literature;[34,35] in the rest of the cancer groups, the correlation was negative (longer time at stages I-II and shorter at stages III-IV) or there was no correlation.[34]

In this regard, Halpering et al. described that stage I-II medulloblastomas were diagnosed in 8 weeks and that medulloblastomas at advanced stages (III-IV) in shorter time (median of 4 weeks),[36] a situation also found by Saha[37] and Brasme et al. for Ewing's sarcoma.[38]

In a study conducted by our group on Hodgkin's lymphomas epidemiology, in tumors with less aggressive histology, TTD was longer (26 and 18 weeks in histological subtypes with predominance of lymphocytes and nodular sclerosis, respectively), whereas in those with more aggressive histology, it was shorter (12 and 6.5 weeks for histological subtypes with mixed cellularity and lymphocyte depletion, respectively).[39] It is therefore suspected that TTD has a higher correlation with biological behavior (tumor aggressiveness) than with stage at diagnosis.[36,40]

Finally, it is important remembering that leukemias are disseminated diseases given the involvement of blood; therefore, a prompt diagnosis does not by nature imply a localized neoplasm (I-II).[38,40]

Time to diagnosis and prognosis

In recent years, studies have been reported analyzing whether a short oncological TTD (≤ 4 weeks) influences on pediatric patients survival prognosis;[18] it has not been possible for prolonged time to be related to shorter survival.

This observation had already been pointed out in 2001 by Halpering et al.[36] and in 2012 by Brasme et al.[38] One explanation was the higher frequency of highly aggressive tumors with higher growth rates in patients with less time to diagnosis. The lack of correlation between TTD and survival has motivated for

the premise that the shorter the TTD, the longer the survival to be questioned.[35,41,42,43] Similarly, in disseminated neoplasms at diagnosis, such as leukemia, several authors[44-46] failed to find greater survival in patients diagnosed in shorter time. The prognosis was related to the type of leukemia and its risk classification.

The survival prognosis depends on the stage at diagnosis and on adequate comprehensive treatment being offered to children with cancer.

Strategic implications of time to diagnosis

Studying and analyzing oncological TTD in children is justified by the implications on actions or strategies to shorten it, and, especially, by the intention to improve survival and quality of life. In this regard, in Mexico, diffusion actions have been carried out about cancer-associated signs and symptoms for early recognition by relatives, as well as for suspicion by doctors.[3]

In the international sphere, courses on childhood cancer early detection have been implemented for family doctors and pediatricians, and even clinical practice guidelines for "opportune" detection have been generated and disseminated, without the concept of opportunity being specified, although detection at early stages is inferred.[10]

Finally, strategies have been designed to accelerate the referral of patients with suspected oncological processes, which thus far have not been assessed or there are no reports about them; moreover, it is not known if they have served to increase survival of children with cancer. Hence the need to comment the questionings that have arisen about the real impact of possible time to diagnosis shortening on mortality reduction in children with cancer;[43] which is why we expound 6 aspects:

1. In Mexico, the time associated with the family members is not substantially different from that reported worldwide. In general, parents usually seek medical care for their child as soon as they detect some data or symptom. On the other hand, compliance with the recommendation on the frequency of evaluations of the healthy child is enough for a doctor who meticulously explores to detect the presence of any tumor. An "over-message" to the population can generate excessive assessments and unnecessary laboratory and imaging testing. The only strategy reported to be successful in spreading information on symptoms of alarm in children was one implemented in Honduras, where mothers were encouraged to observe their babies' eyes, especially in the vaccination campaigns, to detect leukocoria. With this strategy, retinoblastoma diagnosis was achieved at more localized stages.[47]
2. When a patient has enough symptoms as to think about cancer (evident tumor, significant bleeding or persistent fever, among the most common), diagnosis is usually prompt. Kundra et al.[48] recorded 18 % of cases diagnosed at emergency departments and due to symptomatology poor evolution; in another report, the frequency was 25 %.[19] The problem is data subtleness, which 90 % of the time are due to trivial pathology, and owing to their persistence or progression neoplasm is suspected. The United Kingdom tried a strategy known as "Two strike and go":[49] if a patient was assessed more than twice for the same reason and there was no improvement or there was worsening, authorization was given for immediate consultation at a cancer center. At 5 years of implementation of this strategy, unnecessary consultations increased and the rate of oncological diagnoses decreased, without the stages at solid tumors diagnosis being modified. Moreover, even with diagnostic errors, TTD influence on final survival has not been able to be demonstrated.[21] Nevertheless, guidelines continue being generated to facilitate diagnostic suspicion,[49] even when they have not been shown to shorten referral time or decrease diagnosis at advanced stages.

   In view of the failure of this type of strategies, we recommend establishing the diagnosis promptly if the resources to do it are available, otherwise it is preferable to refer the patient to a cancer center as soon as possible. This will enable to initiate a treatment in shorter time, but will not ensure for the patient to arrive at an early stage and perhaps neither a favorable prognosis.
3. A common problem in the care of a child with suspected cancer is the handling of information with the family. Both not establishing a diagnosis and informing about a cancer when it is not, will generate negative behaviors in the family (anger, disappointment, anxiety, demand, among the most common).[50] Therefore, we recommend not being categorical until enough evidence is available.
4. In Mexico, the lack of success in increasing survival for children with cancer has been attributed to the high rate of cases diagnosed at advanced

stages (III-IV). At the Mexican Institute of Social Security, cases at these stages have been reported with variations of 31.6 % for retinoblastomas, 67 % for Wilms tumors and 72 % for non-Hodgkin lymphomas,[2] proportions that are very similar to those reported in developed countries: in the United Kingdom, 49.5 % of stages III-V were reported for Wilms tumors,[51] in the United States, 36.3 % of stages III-IV for Hodgkin's lymphomas,[52] and in Switzerland, Schindler et al. reported metastatic stage (IV) in 27.7 % of the studied childhood cancers.[53] Nevertheless, 5-year survival in these countries is high (> 80% in the United States), as a consequence of the introduction of highly-effective oncological treatments.[33] Therefore, indicating to parents that a child has a poor prognosis due to the delay at which he/she was brought to the doctor will generate unjustified guilt feelings.

5. Immediate reference strategies are correct, especially when there are clinical data consistent with risk for irreversible complications or death. In this regard, patients with solid tumors are usually referred to emergency departments rather than those with leukemia, out of which 70 % are initially seen by first-contact doctor,[54] which demonstrated that there is the possibility to carry out studies prior to referring the children to an oncology department. Hence, we insist on studying them if resources are available. On the other hand, it will be more efficacious for the treatment of these children to invest on the training of emergency physicians for the management of complications associated with oncological treatment, such as febrile syndrome with neutropenia,[55] among others.
6. Finally, the advances in the survival of children with oncological conditions are due especially to chemotherapeutic treatments, a condition not seen years ago when Dr. Aguirre launched his crusade. Numerous regimens have relied on standardized and controlled protocols in multi-center and multinational trials, but also on the investment of resources for patient and family support during the onset of treatment-inherent complications.[33] Hence the emphasis on cooperation programs with international centers,[56] with which resources, hospitals and training of the health team involved in pediatric cancer care are shared,[57] as well as on continuing with the study of potentially modifiable risk factors.

Conclusions

Success in the cure and survival of children with cancer is a reality and has been independent of the high rate of advanced stages or disseminated disease at diagnosis (particularly for leukemias and lymphomas) and it is not related to TTD. The main responsible factor has been the specific antitumor treatment and medical support for complications. Therefore, although it is advisable to favor establishing diagnosis as soon as possible, the pillar of success is comprehensive treatment; therefore, financial resources in Mexico should be focused on it in children with cancer.

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