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Clinical Practice Guidelines for Early Detection, Diagnosis, Treatment and Monitoring of Acute Lymphocytic Leukemia in Children and Teenagers in a Developing Country

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Introduction

Acute lymphocytic leukemia (ALL) is the most common cancer in children; approximately 30% of the malignant tumors in children are acute leukemia, and 75% of them are ALL. In Colombia, the incidence rate (IR) for pediatric cancer and for acute leukemia is 141.2 and 60.1/per year/million people, in children younger than 15 years, respectively. There are approximately 2000 new pediatric cancer cases every year, and 800 of those are ALL [1]. By having the goal of reducing mortality and improving the chances for early diagnosis and treatment for children affected by this condition, the Science Technology and Innovation Government Office (COLCIENCIAS), in conjunction with the Ministry of Health, promoted the development of Clinical Practice Guidelines (CPG) for acute leukaemia in children and teenagers in order to provide recommendations regarding the management for Pediatric patients suffering from ALL and Acute Myeloid Leukaemia (AML) [2]. The risk factors and early detection sections apply to all levels of the healthcare system, led by general practitioners, paediatricians and family physicians, nurses and other basic healthcare personnel. Clinical aspects of diagnosis, treatment, prognosis and monitoring apply only at the level of the centres of high complexity, having units of pediatric haematology oncology and specialized medical and infrastructure for specialized care.

Material and Methods

The Colombia Secretary of Health and Human Services has developed Guidelines to different diseases, including Childhood acute lymphoblastic leukaemia; all GPC in Colombia health services should follow the recommendations of this manual [3].

Following agreement on the objectives of the GPC, we have brought the most relevant aspects related to clinical risk factors, laboratory tests, and issues related to the treatment and monitoring as the starting point of the guide. After this process we have created a flow chart of clinical decisions and then develop preliminary questions for each aspect.

We have described several results as well as the level of evidence and the feasibility of measuring results; we build a list of results and selected the most important in terms of their relevance and usefulness to measure the expected results on the implementation of the recommendations of the GPC. With selected final results and the approved clinical questions, the PICOT format was used to summarize the research topics that explore the effect of therapy. PICOT means: City/Problem Patient, Intervention, Comparison, Outcome, and Time. The guidelines provide the best available evidence to make recommendations for patients pediatric ALL and AML; the system of Scottish Intercollegiate Guidelines Network (SIGN) for the formulation of recommendations on the clinical aspects of risk factors, diagnosis and monitoring was used, the classification of Recommendations Development Evaluation and Assessment System was used (GRADE) for treatment, as grade only it has been validated for this type of clinical question. Recommendations related to issues with contradictory, controversial or insufficient evidence, or where there was a lack of evidence, have been developed using the method of formal consensus license reasonable and non-discriminatory (RAND).

An important aspect in the guidelines process were patient perspective, which was considered four times during the process: prior to the formulation of recommendations for the review of the literature search of references that explore the values of patients and their families related to ALL, in generating recommendations including specific recommendations on important for patients aspects, taking into account their values and preferences in the care process of the disease in order that the professional caregiver to be aware of them and during the publication of the first draft and the final text, groups of patients

received the preliminary final version of the documents and the GDG proceeded to collect and analyze the comments of the participating groups.

For the formulation of recommendations, efficiency is a fundamental result but also adverse events such as toxicity of treatment and late effects should be evaluated. The lack of convincing evidence and few randomized controlled studies led the group to include observational studies that brought up some challenges.

A protocol for systematic literature review includes updating systematic reviews identified with good quality. In general, the protocol consisted of the following sections: (A) Clinical aspect: included clinical questions to address all aspects; (B) Objectives: brief description of the objectives of the review in each clinical aspect; (C) Criteria for inclusion and exclusion of studies; (D) Information sources: databases used and start dates search for systematic reviews; (E) The search strategies: identification of MeSH terms and keywords to search different databases; (F) review methodology: no description related to the way it was elected and evidence for each qualified clinical appearance.

Results

A Guidelines Development Group (GDG) was conformed, it was a multidisciplinary team integrated by alliances between academy, scientific associations and clinicians, the group also included health economists, nurses, psychosocial support caregivers and patient associations. The definition of scope and objectives was developed and carried out from a consensual agreement between the Ministry of Health and the GDG. The selected and prioritized topics were those involving increased morbidity, mortality, health-care infections, medical-surgical complications and quality of life of users, around these problems preliminary questions were formulated. A map-making clinical management of the disease was created from which the preliminary questions were generated.

A systematic search of available Clinical Practice Guidelines national and international was done, then they were rated by four evaluators, using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument, and a final qualification of the global quality of the guideline was obtained. With the information related to the overall quality of each guide and identification of domains with the AGREE II instrument, a non-formal consensus meeting was conducted with the team in order to determine whether guidelines existed to adapt or if the guide should be conducted de novo.

Consistent with the previous process the GDG decided to develop a de novo guideline since there were not found appropriate quality clinical practice guidelines with relevant aspects to allow an adequate adaptation to the Colombian context.

The GDG elaborate a complete guideline for health professionals, and a short guide for ALL. For the ALL guidelines we developed 74 recommendations in 10 aspects. The topics and the number of recommendations (n) were: for Early detection (one), Procedures in case of suspected acute leukemia (four), clinical signs and symptoms for primary care (one), risk factors for acute leukemia (six), diagnosis of ALL (eleven), risk stratification for patients with confirmed diagnosis of ALL (one), diagnostic confirmatory probes for ALL (five), general aspects for ALL treatment (thirty four), monitoring for patients with ALL (seven), factors related to late effects (four).

Some of the recommendations were:

1. For risk factors:

- Avoid prenatal exposure to X-rays and any exposure during pregnancy or early childhood to pesticides, fungicides. Grade of recommendation: B
- Children that weight more than 4000 grams at birth should be monitored by their treating physician [4,5]. Grade of recommendation: B.

1. Diagnosis of ALL: for confirmed diagnosis of ALL, the GDG developed a workshop with 20 experts in pathology, hemato-pathology, pediatric pathology, pediatric oncologist and hematologist, in order to define the recommendations by consensus of experts. For all patients, taking a sample from peripheral blood, bone marrow aspirate and biopsy to confirm diagnosis is mandatory. All patients should undergo morphological, immunological, genetic analysis and molecular biology. Strength of recommendation: Strong in favor. Make morphological diagnosis with bone marrow smear counting 500 cells. Strength of recommendation: Strong in favor. Conventional cytology in cerebrospinal fluid is necessary to determine the central nervous system compromise in patients with ALL. Strength of recommendation: Strong in favor [6,7]. Risk stratification for patients with confirmed diagnosis of ALL: patients with ALL must be stratified by risk, using clinical and laboratory aspects [8]. Strength of recommendation: Strong in favour.

2. General aspects for ALL treatment; Teenagers should be treated with pediatric protocols. Strength of recommendation: Strong in favour. All patients must receive an induction phase as soon as the diagnosis is confirmed and a post induction therapy. Strength of recommendation: Strong in favour. For patients at low risk group, management protocols with lower intensity and/or dose with a single cycle of re-induction. Strength of recommendation: Strong in favour. Patients with ALL should maintain the continuity of the treatment protocol without unjustified delays. Good practice. Prednisone must be used as steroid in all patients diagnosed with ALL in the induction phase no matter the risk group. Strength of recommendation: Strong in favour. For low-risk patients during the induction phase two doses of daunorrubicin and for intermediate and high four doses of daunorrubicin (30 mg/m^2). Strength of recommendation: Strong in favour. The total cumulative dose of anthracycline should be less than 300 mg/m^2 due to the cardiotoxicity risk. Strength of recommendation: Strong in favor. Anthracycline continuous infusion between 6-24 hours in order to reduce cardiotoxicity, also myelotoxicity should be monitored. Strength of recommendation Strong in favour. Intensive post-induction chemotherapy for all patients is

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independent of the risk [9]. Strength of recommendation: Strong in favour. Treatment with phases of consolidation, re-induction and maintenance for all patients. Strength of recommendation: Strong in favour. Methotrexate dose of 5 g/m^2 24-hour infusion in the consolidation phase for T lineage ALL patients and high risk. Strength of recommendation: Strong in favour [10].

3. Measure serum methotrexate levels in patients receiving methotrexate doses of 5 g/m^2. Good practice. For all patients, during the maintenance phase, should receive mercaptopurine (50-75 mg/m^2/day) and methotrexate (20 to 25 mg/m^2/week). Strength of recommendation: Strong in favour. The use of colony-stimulating factor granulocyte as adjunctive therapy in pediatric patients with ALL is not recommended. Recommendation by consensus of experts.
4. Late effects: Monitoring for all patients treated with chemotherapy and/or radiotherapy due to the risk of developing sequels: short stature, osteonecrosis, obesity, diabetes, abnormal sexual development or other hormonal disorders, which must be assessed by pediatric endocrinology. Grade of recommendation: B.

Patients treated with chemotherapy and/or radiotherapy must be followed by pediatric oncologist or trained physicians due to the risk of second neoplasms. Grade of recommendation: C

Educational institutions must offer to surviving patients all the conditions and support according to their necessities during and after therapy [11,12]. Good practice. Another component of the CPG, was a complete and detail guide for parents, patients and caregivers, it was developed by a sub-group of specialists: pediatric hematologist/oncologist, nurses, psychologists, social worker, teachers, parents and children who have lived with leukemia, among others; includes information about leukemia, types of leukemia, clinical manifestations to advice the importance to visit a doctor, the different tests/procedures to confirm the diagnosis and the treatment options (chemotherapy, radiotherapy), side effects, bone marrow transplant), health issues during the treatment as well as the follow up during and after the end of it.

The guidelines include indicators, there were 9 indicators recommended for follow-up in patients with ALL. A big challenge was the initial implementation, it implied changes in public health policies, such as the development of strategies to improve the access to continuous therapy, tools to accurate diagnosis, and work around the available treatment, with the expectancy that the overall survival can reach international standards. At the moment we don't have data about the changes in survival and other outcomes attributable to the implementation of tis CPG.

Nowadays we have been nearly 4 years since the development of the guidelines, it was not implemented by all the pediatric oncology units in Colombia, but it was for the majority. Only a hospital made an evaluation about adherence and compliance for these guidelines, and the results were 98%. Related to the indicators, seven of them were fully compliant in most institutions; 2 of them, both which related to early diagnosis using the Comprehensive Attention for Prevalent Infant Diseases strategy (AIEPI in Spanish), were not possible for the pediatric oncology units to know how many or which proportion of patients were evaluated using this tool, this document is used regularly by the primary care levels since this year [13,14].

Discussion

In Colombia the overall survival for acute lymphoid leukemia is around 50% while in other countries is near 80%, to reduce this gap in survival for our patients in Colombia, the Ministry of Health considered the elaboration of CPG for acute pediatric leukemia as a strategy to diminished the heterogeneity in the clinical practice, to standardize the management of childhood hematological cancer looking for get best survival rates.

The pediatric clinical practice guidelines developed in Colombia were evaluated by a group of investigators in 2015, they evaluated seven CPG including asthma, diarrhea, congenital anomalies, premature newborn, healthy newborn, perinatal asphyxia, respiratory disease, sepsis, pediatric lymphomas and acute pediatric leukemia. The Appraisal of Guideline Research and Evaluation (AGREE II) tool was used; reviewers assessed each domain and graded using a scale from 0-100%. The level of agreement between raters was assessed using the intra-class correlation coefficient [4-6].

The CPG for leukemia obtained the highest score. The agreement between raters was very good for most domains. Six domains were considered: objective, participation of relevant population (physicians, patients, and providers), rigor in elaboration, clarity of presentation, applicability and editorial independence. For the acute leukemia CPG, most domains were over 94%, with 4 domains over 98%. The domain related with elaboration is the one considered by some authors as the most important to determine quality and validity of the guidelines, for pediatric ALL this domain has 95%. Another good qualification for these guidelines was an adequate plan for implementation, and the description of possible applicability barriers. The assessment of the guidelines show, that they have a high quality and, therefore, it´s recommended for use in clinical practice.

Conclusions

CPG is a good strategy to diminish the heterogeneity in the clinical practice of some diseases. Currently nearly 70% of the country is using the CPG, but not all the pediatric oncology units are doing evaluations related to compliance.

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