Childhood acute myeloid leukemia: how are we doing in Brazil?

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Pediatric oncology is the sub-specialty which has advanced the most over the last 30 years. A period during which the majority of the specialist centers in Brazil were inaugurated. At all of these centers, leukemias occupy a position of prominence among malign diseases, being predominantly (95-98%) acute. Lymphoid leukemias make up 70 - 80% of these. Of the chronic forms of leukemia, only myeloid is manifest among children and adolescents.

There are three pathologies that are frustrating to those who work in pediatric oncology in terms of survival: neuroblastoma, acute myeloid leukemia, and central nervous system. The first two because of the unsatisfactory rates achieved even nowadays and the third because of the quality of that survival. We have been working with survival rates above 70% for almost all malignancies, and the fact that we come face to face with rates that oscillate around 30 - 40% is, on one hand, discouraging, but on the other hand it stimulates us to fresh research in an attempt to discover what goes on in the interior of a malignant cell that makes it more or less aggressive and more or less responsive to chemotherapy and radiotherapy.

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The relevance of the work presented by Prof Marcos Borato and colleagues (BH/MG)[1] is in showing us the behavior of acute myeloid leukemia at a center of excellence, a report that has been rarely described among us.[2] The current paper tells us of patients less than 16 years old. The ideal nowadays is to care for young people until they are 19, or even 21 as already happens overseas. I draw attention to this fact because every day more articles appear on cancer in the adolescent and we have to modify our learning at the point at which we look at the incidence and behavior of malignant diseases in this age group, particularly in relation to patients from 15-19, an age-group that is not dealt with in the current paper.

A precise classification of leukemia is the starting-point for suitable treatment to improve prognosis. Since 1976, French, American and British specialists have been publishing the FAB classification. This is essentially morphological, and was revised in 1985, becoming the benchmark of acute leukemia study. In this classification, acute lymphoid leukemias (ALL) are divided into L1, L2, and L3. Myeloid forms were initially classed as M1(without maturation), M2 (with maturation), M3 (promyelocytic), M4 (myelomonocytic), M5 (monocytic), M6 (erythroleukemia) and M7 (megakaryoblastic) and then the subtype M0 (no differentiation) was added. Exclusively morphological analysis is often inadequate to an exact determination of cellular lineage. Cytochemistry then joined the ranks as an additional method that can increase diagnostic accuracy. Later other methods were added, and nowadays immunophenotyping is indicated in all acute leukemia cases with the objective of making a precise diagnosis, avoiding morphological interpretation errors which confuse ALL with certain subtypes of LMA. Performed with monoclonal antibodies, this technique has both the high specificity and the sensitivity necessary to differentiate them.

In 1988, the Second MIC Cooperative Study Group. Morphologic, immunologic and cytogenetic (MIC) working classification of the acute myeloid leukemias was published[3] and it was established that this system had greater clinical significance than the FAB categories, since the association of the variables used provides more detail for each leukemia patient allowing us to form groups with distinct prognoses. In 1998, Bain[4] published new work in which it was shown that molecular genetic studies (MIC-M) would have to be incorporated into acute leukemia classification. Today we know that cytogenetic and genetic anomalies are more

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important both to prognosis and the choice of treatment than morphological characteristics or even immunophenotypes. Seventy to eighty percent of patients with LMA exhibit clonal cytogenetic abnormalities. Papers relating these abnormalities to prognosis have been multiplying. It was this type of research that showed us that LMA subtypes could be treated differently in the future. This is already so in the case of LMA M3 (promyelocytic), which is treated with trans-retinoic acid and chemotherapy.

The research that Borato et al. have described is founded on morphological classification, which used to be habitual in this country, and for this reason we cannot evaluate the survival of their patients in terms of all the prognostic factors known today.

The large-scale, international leukemia study groups published their protocols and results. Overall the Germans achieved the highest survival rates and their teachings were spread all over the world: the BFM protocols (Berlin-Frankfurt-Munich) are followed by a large number of services, being adapted by a large number of them.

The undeniable need to treat these patients within rigid protocols and progress in the fight against infections that systematically target these patients have meant that, after the last three decades, we are reaping rewards in terms of survival rates. Pediatric oncology has been outstanding for the discipline with which it has followed these protocols, as Schiffer pointed out in an editorial in the Journal of Clinical Oncology,[5] the official organ of ASCO (American Society of Clinical Oncology).

The arguments continue: should maintenance therapy be given or not[6]? Is stem cell transplantation indicated? From which source? When[7,8]? How should drug resistance and minimum residual disease be routinely tested?

There have been studies demonstrating increased myeloid blast resistance to a number of different drugs, including etoposide,[9] which was used with one group of the patients studied by Borato et al, and later abandoned due to poor results.

We do not know in detail what goes on in our country. Incidence and clinical manifestations are distinct. In Bahia, there appears to be a greater incidence of LMA (30-35% of acute leukemia cases) with frequent extra-medullary presentation (known as “chloromas” or “granulocytic sarcomas”). However, we have important progress to announce: classes have already started to become more refined. Within the country eight Laboratories of Excellence are being set up (three are already functioning) with the support of the Fundação Banco do Brasil Child Life Program in collaboration with the Health Ministry. Extremely recently we began to use all of the leukemia classification methods. Furthermore, the Brazilian Pediatric Oncology Society (SOBOPE - Sociedade Brasileira de Oncologia Pediátrica) has formed the Brazilian Cooperation on Pediatric Oncology Group (GCBOP Group Cooperativo Brasileiro em Oncologia Pediátrica) which has cascaded our protocols to the national services (www.sobope.org.br). The Brazilian College of Hematology has begun a National Acute Myeloid Leukemia Registry (cbh@pegasus.fmrp.usp.br).

Important challenges remain yet: to reduce the mortality rate during the initial phase of treatment (remission induction), almost always due to infection or hemorrhagic complications, to achieve adequate hospital support (extremely high costs!) bearing in mind that 85 -90% of our patients come to us on the Sistema Único de Saúde (Brazilian National Health System), to equate our results with those of the world scientific literature,[10] to minimize the toxicity of the drugs used, at long and short term and to better understand infant leukemia,[11] among others. There is still a long way to go.

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