líticas, sem dúvida alguma envolve a implantação de um programa de hemácias fenotipadas na rotina transfusional. O programa de hemácias fenotipadas e, em especial, a manutenção de um estoque de sangue fenotipado, continua sendo ainda questionado devido ao custo e trabalho que demanda. A decisão da implantação do programa deve levar em consideração o índice de aloimunização nos pacientes transfundidos e a dificuldade na obtenção de sangue fenótipo compatível no momento da transfusão. Vale a pena salientar que a fenotipagem de doadores, quando realizada na rotina utilizando-se microtécnicas, muitas vezes automatizadas, leva a uma redução de custos e maior qualidade no procedimento.

Apesar de existirem ainda algumas questões não respondidas em relação à resposta imune a antígenos eritrocitários, acredito que a implantação de protocolos seguros e eficientes de fenotipagem e/ou genotipagem de grupos sangüíneos pode reduzir drasticamente os riscos de desenvolvimento de aloanticorpos em pacientes que recebem transfusão sangüínea. No futuro, a utilização de plataformas automatizadas e seguras de fenotipagem e/ou genotipagem em larga escala pode representar um grande avanço na segurança transfusional.

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The importance of the detection of MRD at the end of induction chemotherapy in childhood ALL

O valor do estudo da doença residual mínima no fim da indução na LLA da infância

Irene Lorand-Metze

Pediatric ALL is one of the most curable cancers nowadays. Therefore, modern treatment protocols aim to cure the largest number of patients producing the least number of late side effects. Historically, multicentric trials stratified treatment of patients using clinical, laboratory and molecular features at diagnosis that were well-know prognostic factors. Among them, the velocity of peripheral blood and bone marrow clearance of blasts during induction therapy was recognized a long time ago as being very important in the outcome of patients.

The concept of minimal residual disease (MRD) in ALL was established in the 90s[1,2] based on phenotypic and molecular features of the leukemic cells. The analysis of phenotypic features is based on the knowledge that neoplastic cells have over- or under-expression of antigens, asynchronous expression of maturation markers or expression of cross-lineage antigens.[3] Thus it is possible to distinguish normal and neoplastic cells in about 85% of the cases of ALL. This method became well established with the development of multiparameter flow cytometry, where the concepts of "positive" and "negative" as well as "% of positive cells" were abandoned. Multiparametric analysis (using 3 or more colors) allows electronic separation of the several subsets of cells in a sample, including rare populations, by their physical and antigenic characteristics.

The state-of-the-art of flow cytometric analysis in acute leukemias are 3 color whole blood platforms that can be easily performed using a conventional one-laser flow cytometer that is available in most Brazilian centers that treat ALL. Hence, the old panels, usually containing 20-30 antibodies analysed using one or two color platforms were substituted by a few 3 or 4 color combinations thereby drastically decreasing costs and rendering this technique cheap, fast and feasible for a large number of patients in multicentric clinical trials.[4]

The work by Delbuono E *et al*.[5] published in the current issue demonstrates the feasibility of a simple, although very sensitive, measurement of MRD during the induction treatment of pediatric ALL. The authors use a procedure similar to that developed by the St Jude Children's Hospital and validated by a group in Recife. This technique is able to detect one leukemic cell in 10^4 peripheral blood or bone marrow cells. The presence or absence of MRD at the end of the first month of treatment of pediatric ALL is currently the most important feature to predict event-free survival of patients, and is an independent prognostic factor across all traditional ALL risk groups.

On the other hand, molecular techniques were initially based on the detection of several gene rearrangements whose frequencies are usually less than 10%. Therefore a large number of tests were necessary in order to find a molecular marker that was suitable to detect MRD at the end of induction. This was more recently replaced by quantitative PCR analysis of patient-specific immunoglobulin and rearrangements, which may detect one in 10^4 leukemic cells in 85-90% of ALL cases. However, these techniques are time-consuming, logistically demanding and relatively expensive requiring regular inter-laboratory quality control.[6] For this reason, even large multicenter study groups such as the Children's Oncology Group 2 and many countries in the ALL IC-BFM consortium prefer to assess MRD by flow cytometry which is able to give real-time information about the necessity of reducing or intensifying consolidation therapy.

All studies that quantify MRD at the end of the first month of treatment of ALL, regardless of the technique used, are able to detect 10%-15% of patients (MRD-negative in peripheral blood on day 8 and in bone marrow on day 29 or 33) presenting 90% of cases with event-free survival in 5 years using very low toxicity chemotherapy. Conversely, patients with a high risk of recurrence may also be detected, identifying the need of further treatment and improving outcomes.

There are efforts, including in Brazil, to improve and simplify molecular techniques for MRD, but usually flow cytometry is preferred even in large multicentric trials.[2,6-8] Therefore, the paper by Delbuono E *et al*.,[5] proving the feasibility of a simple flow technique is very important. It would be interesting to know the outcomes and the role of the detection of MRD in their group of patients.

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Allogeneic bone marrow transplantation for severe aplastic anemia patients with risk factors poor prognosis: is fludarabine a requirement?

Transplante de medula óssea alogênico para pacientes com anemia aplástica grave de mau prognóstico: fludarabina é necessária?

Frederico L. Dulley

Bone marrow hematopietic progenitor cell transplantation is a curative treatment for severe aplastic anemia.[1] Many attempts have been made to decrease rejection after transplantation adding antithymocyte globulin to the conventional dose of 200 mg/kg cyclophosphamide,[2] or total body irradiation at 300 cGy in one day[3] or low dose of busulfan 4 mg/kg in one day.[4] All these regimens have been proven to decrease rejection in patients who had been submitted to transplantation.

The question that raises concern, of Medeiros CR *et al*.[5] as published in this issue, is whether fludarabine is a requirement in the conditioning regimen. The answer is probably no.

This answer is based on two observations: first, the results published by Medeiros CR *et al*[5] using cyclophosphamide and busulfan are very good in this population