

Central nervous system therapy in acute lymphoblastic leukemia: no more, no less

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Central nervous system (CNS) infiltration at diagnosis remains a poor prognostic factor in acute lymphoblastic leukemia (ALL) with over 30% of relapses involving CNS. Treatment with antileukemic agents against CNS leukemia is an essential component for cure in ALL. With the intensification of CNS-directed therapy, cranial radiotherapy (CRT) has been completely omitted in current pediatric ALL protocols, or limited to a minority of high-risk patients, without an increase in relapse rates.¹ Avoiding CRT is an important step forward due to its long-term adverse effects, such as endocrinopathies, neurocognitive deficits, and second cancers. Nevertheless, contemporary intensive systemic and intrathecal (IT) chemotherapy is also associated to short- and long-term neurotoxicity and it seems to be a threshold dose effect for the association between IT chemotherapy exposure and cognitive impairment, particularly in younger children.²

The intensity of conventional chemotherapy has reached its limit in current therapeutic protocols, with the rate of toxic deaths approaching that of deaths from relapse in pediatric patients with ALL.¹ Concerns about acute and delayed toxicity in children treated with intensive treatment has changed the focus in new protocols of therapy aiming to avoid undertreatment, but also overtreatment.

Possible overtreatment of patients with low levels of leukemic CNS involvement (CNS2) is analyzed by Heilmann and colleagues in this issue of *Haematologica*.³ They assessed the effect of three versus five doses of IT methotrexate (MTX) in induction therapy on systemic toxicity in children and adolescents with ALL aged 1-17 years. In a retrospective analysis of 6,136 patients enrolled in the AIEOP-BFM 2009 clinical trial, the authors found that the addition of two extra doses of IT MTX in patients with initial CNS involvement (CNS2 and CNS3) was associated with a significant increase in life-threatening and fatal infections. Patients with CNS2 or CNS3 involvement who received five IT MTX showed an incidence of life-threatening and fatal infections of 4.4% and 1.6%, respectively, versus 1.6% and 0.3%, respectively, in patients receiving three

doses. The authors attributed this increase in infections to the systemic effect of IT MTX. Although the group of patients with CNS involvement also had other factors associated with an increased risk for infection (such as age > 10 years or dexamethasone therapy in induction), having received these two additional doses of IT MTX was the strongest risk factor for severe infections in the multivariate analysis (Odds Ratio [HR]: 2.85; 95% Confidence Interval [CI]: 1.96-4.14; $P < 0.001$). CNS3 status was associated with greater risk for relapse in B-cell precursor (BCP) ALL (HR: 1.59; 95% CI: 0.85-3.0; $P = 0.15$) and in T-ALL (HR: 2.65; 95% CI: 1.56-4.51; $P < 0.001$), but CNS2 status was not. Based on the severe adverse events associated with the intensification of IT therapy in patients with CNS involvement at diagnosis, and the unclear relevance of CNS2 for relapse risk, the number of intrathecal doses has been reduced in patients with CNS2 involvement in the current AIEOP-BFM ALL 2017 treatment protocol.

Frank CNS infiltration (CNS3) is an adverse prognostic factor in pediatric ALL patients. However, the impact on outcome of CNS2 is controversial and varies between different treatment groups and protocols, and according to ALL immunophenotype. The uncertain value of CNS2 may be due to several reasons. First, there are differences in systemic and CNS-directed treatment, which includes cranial radiotherapy in high-risk patients in some protocols that can modify, and even abrogate, the prognostic impact of low levels of CNS leukemia. Thus, in some clinical trials in which CNS-directed therapy was not modified in CNS2 patients, CNS2 status had an adverse prognostic impact.⁴ In this regard, the Children's Oncology Group (COG) published their results from three clinical trials in which patients with BCP-ALL with CNS2 involvement had higher CNS relapse rate and lower 5-year event-free survival (85% vs. 76%; $P < 0.001$).⁵ In these treatment protocols, patients with CNS2 did not receive extra doses of IT therapy. However, in other clinical trials, in which patients with CNS2 received additional doses of IT chemotherapy during induction, CNS2 lost its prognostic significance^{6,7} or only

retained its significance in T-ALL.¹ Of note, CNS2 status did not have any adverse prognostic impact in patients treated with the AIEOP-BFM ALL 2009 protocol, as reported by Heilmann *et al.* in this issue of *Haematologica*.³ However, as these patients did receive two additional intrathecal doses, we cannot rule out the possibility that their omission might increase the risk of relapse.

Second, there might be differences in the prognostic value of CNS involvement across different biologic subgroups of ALL, in which the modification in therapy may have a different impact.¹ Indeed, unlike BCP ALL, CNS2 status did not have any impact on outcome in T-ALL patients treated according to augmented BFM therapy in the COG AALL0434 and AALL1231 clinical trials.⁸

Finally, the incidence of CNS2 status varies widely between groups (from 2.4% to 42%), probably due to pre-analytical and analytical factors rather than to true clinical differences.⁹ The way of stratifying CNS, based on leukocyte and red blood cell counts in the chamber together with a cytologic study of the cyto-centrifuged CSF sample has low

sensitivity, specificity, and reproducibility. This heterogeneity makes it difficult to compare the prognostic value of CNS2 status across trials. Clearly, better methods are required to assess the degree of CNS infiltration at diagnosis, as well as biomarkers to measure response to treatment, as with MRD assessment in systemic disease. In this regard, CSF flow cytometry may achieve greater sensitivity and predictive prognostic value, as recently demonstrated by the Nordic Society of Paediatric Haematology and Oncology (NOPHO) group.¹⁰

The study by Heilmann and colleagues identifies important issues in the management of ALL patients, such as the need to reduce toxicity and improve stratification of CNS leukemia. Better biomarkers of CNS disease that allow administration of the right dose to prevent relapse are required to avoid overtreatment and toxicity. No more, no less.

Disclosures

No conflicts of interest to disclose.

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