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Haematologica 2021 [Epub ahead of print]

Citation: Valentino Conter and Francesco Ceppi. Are clinical pharmacology studies still needed in childhood acute lymphoblastic leukemia?
Haematologica. 2021; 106:xxx

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Are clinical pharmacology studies still needed in childhood acute lymphoblastic leukemia?

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In this issue of Haematologica, Karol et al. report a study on dose intensities (DI) for all drugs in two consecutive Acute Lymphoblastic Leukemia (ALL) clinical trials at St. Jude Children’s Research Hospital, which differed in their asparaginase formulation, and intensity.(1) The amount of data is impressive, with more than 500 thousand dosing records. The main message of the manuscript is that the lack of benefit from an increased asparaginase intensity may be due to the decrease of DI of other drugs, induced by the additional treatment with asparaginase.

It is widely recognized that intensity of chemotherapy delivered has an impact on outcome and that drugs interaction, difficult to assess, can influence on anticancer activity and on acute and/or late toxicity too. The fast improvement of outcome in childhood ALL in the last 3 decades of the last century were strictly associated with progressive treatment intensity. Dr. Riehm was the pioneer in this historical process, which was thereafter pursued by all major pediatric oncology groups. In the early 90ies, Sallan summarized the DFCI experience, largely based on treatment intensification with asparaginase, with the words “More is better!”,(2) and Niemeyer (with Riehm and Sallan) suggested that merging the intensive elements of BFM and DFCI protocols would be a logical program to improve outcome.(3) Various attempts were made in this frame, sometimes successfully, such as in the CCSG study with Augmented BFM.(4) Most studies however did not show any benefit in intensive BFM-oriented protocols, neither from additional asparaginase treatment (AIEOP ALL 9102) (5), EORTC-CLG trial 58951 (6), NOPHO ALL-2008 (7), BFM ALL 90 (8), nor from the marked intensification in the COG AALL1131 trial with Clofarabine, which was interrupted early due to excess of toxicity.(9)

This general experience has led to a consensus that treatment intensity in childhood ALL may have reached the maximum tolerated doses, so that further improvement can only be obtained by precision medicine based on targeted therapies. However, most children with ALL are
cured with conventional chemotherapy, which can be further optimized and tailored thanks to the progressive improvement of biology-based stratification.

The study by Karol et al. shows that room remains for improvement of chemotherapy, although this cannot be achieved by a simple protocol therapy intensification.(1) Asparaginase is a drug with a unique mechanism of action, for there are no suggested alternatives for replacement in patients who cannot be treated with this drug. Yet, DFCI studies showed that these patients have a poorer outcome. In this context it quite interesting the finding that patients with low asparaginase DI higher systemic methotrexate (MTX) DI compensated for low asparaginase DI. Of note is also the often neglected and yet most relevant aspect of the oral medications administered at home. In the study here reported there is the apparent paradox of higher relapse rate associated with higher DI for mercaptopurine, which, as suggested by the authors, might reflect low treatment adherence for oral medications at home, which was not measured in this study, in keeping with the findings of the Children's Oncology Group AALL03N1 Study, where it was shown that adherence rate below 90% to maintenance therapy was associated with increased relapse risk.(10)

Although the expectation for further improvements in the treatment of childhood ALL are mostly based on innovative immunological or targeted therapies, pharmacological studies remain crucial to improve the therapeutic index of antineoplastic agents combinations. To this purpose, it must be considered that simple measurement of duration of treatment phases, incidence of severe adverse effects, DI of single agents may be inadequate or even misleading. The need is thus for comprehensive investigations on compliance/adherence for all drugs, drugs interactions and bioavailability, and germline and tumor sensitivity, in order to optimize precision personalized treatment in childhood ALL.
References


