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COMMENTARY

Treating second-relapsed/refractory first-relapsed childhood acute myeloid leukaemia: Successful salvage rather than palliation?

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Prognosis of second-relapsed/refractory first-relapsed childhood acute myeloid leukaemia remains poor and there are no clear guidelines on the best treatment approach. The report by White et al. suggests that, while outcomes are still unsatisfactory, there is room to pursue a curative approach rather than palliation.

Commentary on: White et al. Clinical outcomes of second relapsed and refractory first relapsed paediatric AML: A retrospective study within the NOPHO-DB SHIP consortium. Br J Haematol 2022;197:755-765.

KEYWORDS
clinical outcomes, first resistant relapse, paediatric acute myeloid leukaemia

Prognosis of second relapse or first-resistant relapse of acute myeloid leukaemia (AML) remains very poor and no general guidelines or trials are available for this setting. In this issue, White et al.[1] report on the outcomes of some 157 paediatric patients with second-relapsed or refractory first-relapsed AML (i.e., those patients treated with third-line therapies) treated with one of the study protocols of the Nordic Society of Paediatric Haematology and Oncology, the Netherlands, Belgium, Spain, Hong Kong, Israel, and Portugal (NOPHO-DB SHIP). In this retrospective study they found 1- and 5-year projected overall survival (pOS) of 22 (SE 3)% and 14 (3)% respectively, with no differences between refractory first-relapsed and second-relapsed AML. Notably, 5-year pOS reached 37% for those patients (15% of the whole cohort) who received chemotherapy and hematopoietich stem cell transplantation (HSCT) as third-line therapy. These data are in line with those of a similar study by Rasche et al.[2] reporting on a cohort of 73 patients with a second relapse, with 5-year pOS of 15 (4)%. Among factors influencing prognosis, late relapse (defined as >12 months from diagnosis) was correlated with an improved survival, while FMS-like tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD) mutations (not considering those associated with nucleophosmin 1 [*NPM1*] mutations) were associated with worse prognosis.

These data document a change of perspective in the treatment scenario of second-relapse and refractory first-relapsed AML. Indeed, the intent of treatment is no longer only palliative, but a curative aim can be pursued. In this regard, data presented by this study will help physicians to better inform parents on the real prognosis of such patients. One important limitation of the White et al.[1] study, as for most of retrospective (and prospective) studies, is the lack of data on quality of life, which assumes utmost importance in the setting of advanced disease. Indeed, the main dilemma of both physicians and parents in the case of recurrent disease with poor prognosis, especially in case of good performance status of the patient, is if to expose him/her to a toxic regimen as opposed to preserving quality of life, allowing them to spend as much time as possible outside the hospital with his/her family and loved ones.

In an era in which chimeric antigen receptor (CAR) T cells have revolutionised the treatment scenario of B-cell precursor acute lymphoblastic leukaemia, it is not

infrequent that parents of children affected by haematological malignancies ask for a new course of therapy despite advanced disease, asking for 'that new effective treatment for leukaemia'. Although CAR T cells for myeloid malignancies are still in their infancy,[3] new treatments, such as flotetuzumab[4] and magrolimab[5] among others, are becoming available. These promising new therapies will need a benchmark to be better evaluated, and the work of White et al.[1] is certainly a starting point. Notably, as T-cell-based immunotherapies hold the promise to be agnostic to traditional adverse cytogenetic or molecular risk factors (and there may be a faint signal from the studies involving flotetuzumab), it is possible that the prognostic factors found in this study will not be confirmed in studies involving these treatments.

The data presented by the NOPHO-DB SHIP consortium point out, not surprisingly, the central role of HSCT in the salvage strategy of third-line patients, as patients receiving chemotherapy and HSCT had a notable 5-year OS of >30%. Although this result may be biased by the retrospective nature of the study and the lacking of other data, it is not incautious to say that, once the decision of treating the patient has been taken, all fit children should undergo HSCT (irrespective of a previous one, as a past HSCT before relapse did not appear to have a statistically significant effect on survival in this cohort, although this can be the result of biased patient selection and/or sample size). However, no information is present on the type (or even the intensity) of the conditioning used, as well as of the donor employed. Thus, as with many studies, this one generates a number of questions: in case of a previous HSCT is changing the donor a good choice? Is it better to choose a less compatible donor or decrease graft-versus-host disease prophylaxis in order to better exploit the graft-versus-leukaemia effect?.

Another important information lacking is response data to re-induction therapy: do children who achieve a complete response after re-induction have a better prognosis? Possible if not probable. Do we have to put on palliation those who did not respond to re-induction without further proceeding to HSCT? Harder to say. New studies, hopefully prospective, and wider registry studies will help answer these and other questions. Waiting for new, effective, less-toxic treatments that may further improve the prognosis of these patients.

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