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What a wonderful world: beyond relapsed pediatric acute myeloid leukemia

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In this issue of *Haematologica*, Elgarten et al. report a retrospective analysis of 247 children with first-relapse acute myeloid leukemia (AML) using the Real-world Epidemiology of Acute Leukemia–AML (REAL-AML) database, providing a comprehensive overview of the salvage regimens used and their associated outcomes.(1) The database included patients treated at 13 institutions across the United States between 2011 and 2023 and was estimated to capture approximately 15% of pediatric first-relapse AML cases in the United States during this period.

The study reveals remarkable heterogeneity in the treatment of relapsed pediatric AML: 39 distinct salvage regimens were identified, although approximately 80% of patients received intensive therapy. FLA(G) and CPX-351 were the most commonly used regimens. FLA(G)-based regimens, including combinations with anthracyclines, hypomethylating agents, or histone deacetylase inhibitors, accounted for approximately half of all intensive regimens. The use of CPX-351 increased after 2017, likely reflecting the conduct and subsequently favorable results of the COG AAML1421 phase I/II trial, which evaluated the efficacy and safety of CPX-351 and enrolled patients between 2016 and 2018.(2) Gemtuzumab ozogamicin (GO) was incorporated into 24% of intensive regimens. Non-intensive regimens were more commonly used in patients who relapsed after hematopoietic cell transplantation or experienced early relapse within one year of initial diagnosis, and their use increased following the introduction of venetoclax.

Despite this diversity of treatment approaches, no significant differences in response rates or overall survival (OS) were observed according to the chemotherapy backbone. Notably, however, the addition of an anthracycline to FLA(G) was associated with improved OS and higher rates of complete remission (CR) and MRD-negative CR. Similarly, the addition of GO was associated with higher rates of CR and MRD-negative CR, although these improvements in response did not translate into better OS.

Why, then, is relapsed AML so difficult to treat? At the heart of the problem lies the limited armamentarium of effective agents against AML. Cytarabine and anthracyclines remain the key components of AML chemotherapy. However, anthracycline use is constrained by cumulative cardiotoxicity, making further intensification particularly challenging in patients with relapsed disease who have already received substantial cumulative doses during frontline therapy. Consequently,

salvage therapy has traditionally relied heavily on cytarabine, and FLA(G), in which fludarabine enhances the cytotoxic activity of cytarabine, has become one of the most widely used regimens. Yet the efficacy of cytarabine-based therapy has inherent limitations against relapsed AML cells that have acquired greater treatment resistance. The finding that the addition of an anthracycline improves treatment efficacy, demonstrated both in the present analysis and in the Relapsed AML 2001/01 phase III trial conducted by the International BFM Study Group, underscores the continuing importance of anthracyclines in this setting.(3) In this context, liposomal formulations are particularly attractive because of their potential to mitigate anthracycline-associated cardiotoxicity. Liposomal daunorubicin was therefore incorporated into the I-BFM relapse trial (however, it is no longer commercially available), and the liposomal formulation of daunorubicin and cytarabine in CPX-351 has likewise generated considerable interest.(4)

It is equally clear, however, that further intensification or refinement of conventional cytotoxic chemotherapy alone is unlikely to yield major improvements in outcomes. The incorporation of novel molecularly targeted agents and immunotherapeutic approaches is therefore essential.(5) As reflected in the present study, FLT3 inhibitors and the BCL2 inhibitor venetoclax are already being increasingly incorporated into the treatment of relapsed pediatric AML. Considerable enthusiasm also surrounds menin inhibitors, which may be particularly relevant to several poor-prognosis molecular subsets of pediatric AML, including *KMT2A*-rearranged, *NUP98*-rearranged, and *UBTF*-tandem duplication AML.(6) RAS pathway alterations have also emerged as an important mechanism of treatment resistance in pediatric AML.(7) Although RAS was long considered “undruggable,” this paradigm is rapidly changing with the development of innovative RAS-targeted agents. Encouraging clinical activity has recently been reported with daraxonrasib in pancreatic cancer, raising the prospect that direct pharmacological targeting of RAS may eventually become feasible in AML.(8) Translating these advances into clinical trials for AML, particularly for molecularly defined and treatment-resistant disease, represents an exciting avenue for future investigation.

Finally, therapeutic innovation must be accompanied by a clinical trial framework capable of efficiently evaluating emerging treatments. Although approximately 40% of children with AML experience relapse, only about 250 cases of relapsed pediatric AML occur each year across the United States, Europe, and Japan combined, and

fewer than 20% of these patients are enrolled in clinical trials. (9) This challenge becomes even greater with molecularly targeted therapies, as increasingly refined molecular stratification further reduces the number of patients eligible for any given treatment. International collaboration is therefore indispensable for the efficient development and evaluation of novel therapies for pediatric AML. The Pediatric Acute Leukemia (PedAL) initiative represents an important step toward addressing this challenge by establishing an international clinical trial platform for pediatric AML.(10) Studies conducted within this framework include ITCC-101/APAL2020D (NCT05183035), evaluating venetoclax-based therapy, and ITCC-101/APAL2020K (NCT06376162), evaluating the menin inhibitor ziftomenib; Japan is also participating in the former. Such international efforts provide an opportunity not only to improve outcomes for children with relapsed AML but also to accelerate the development of new therapeutic strategies for pediatric AML as a whole.

As this “real-world” study vividly illustrates, the landscape of treatment for relapsed pediatric AML remains complex and unsettled—perhaps not unlike the world around us. Yet, through continued therapeutic innovation and international collaboration, we hope to transform this landscape, improving outcomes for children with relapsed AML and ultimately bringing these advances forward into frontline therapy. Our goal should be not merely to treat relapse more successfully, but to establish therapies that prevent relapse from occurring in the first place. We look forward to a future in which relapse becomes an increasingly rare event for children with AML—a step from the “real world” of today toward the “wonderful world” immortalized by Louis “Satchmo” Armstrong.

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