Pediatric acute leukemias and myelodysplastic syndromes, progress and challenges: introduction to a review series

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The review series on pediatric acute leukemias and myelodysplastic syndromes, published in this issue of *Haematologica*, focuses on the challenges in a field in which much progress has been made during the last decades.

Acute lymphoblastic leukemia (ALL), the most common childhood cancer, is now curable in most patients.[1] Yet the price paid for these cures in terms of short- and long-term toxicities is unacceptable. Barzilai Birenboim and Rabinowicz review the acute therapy-related toxicities beyond immediate infectious complications.[2] Pancreatitis associated with asparaginase is one of the most serious life-threatening complications, as can be events of venous thromboembolism, also associated with asparaginase (but also with other drugs), in addition to genetic predisposition. Several acute neurological complications to methotrexate (MTX) and other therapies are discussed. Delayed MTX elimination can also cause severe systemic toxicities. Osteonecrosis is a serious life-debilitating acute to chronic complication of high-dose steroids therapies. Finally, the emerging toxicities of the new biological therapies are discussed. Although these novel therapies are much less toxic than chemotherapy, they are accompanied by unique immediate and intermediate toxicities. However, it is still too early to evaluate the long-term toxicities of modern immunotherapies.

Two reviews in the series describe the challenges and progress in subtypes of ALL with a particularly grim prognosis. Hughes *et al*.[3] review recent progress in deciphering the landscape of the genomics of relapsed T-ALL and the highly related T-cell lymphoblastic lymphoma, for which overall survival is less than 30%. These studies have revealed novel subtypes of T-ALL and their prognostic significance. A recent study from the same authors has suggested that the presence of early bone marrow progenitor-like cells predicts the poor prognosis of some of these leukemias.[4] The review further addresses the new developments of effective CAR-T cell therapies, currently in clinical trials, providing hope of improving the dismal outcome of relapsed T-cell malignancies.

Infant ALL, commonly driven by KMT2A rearrangements, is another form of ALL with a poor prognosis and this is reviewed by Stutterheim *et al*.[5] The long-term survival of infants with ALL has been less than 50%. Two recent developments are about to change this grim outcome: the incorporation of bi-specific antibody blinatumomab to the treatment protocol, and the development of menin inhibitors that block the oncogenic activity of KMT2A fusion proteins. The authors also review remaining challenges such as central nervous system involvement and the lineage switch that is caused by the pre-lymphoid cell of origin, and which is expected to increase after B-cell specific immunotherapy.

While progress has been made in the treatment of pediatric acute myeloid leukemia (AML), the cure rate is only around 70%.[6] Umeda *et al*.[7] review the current classification of pediatric AML focusing on recent discoveries, by the authors and others, of four subtypes of high-risk AML: *CBFA2T3::GLIS2*, BCL11B structural variants, UBTF tandem duplications (UBTF-TD), and ETS family fusions. Interestingly, similar to KMT2A-rearranged leukemias, UBTF-TD AML also activates *HOXA* genes and responds to menin inhibitors, thus providing hope for the devastating outcome associated with this leukemia.

Pediatric myelodysplastic syndromes (MDS) is the subject of the final review in the series by Kotmayer *et al*.[8] The ethology and the genomic characteristics of primary MDS in children are very different from adult MDS. The former is a developmental hematologic disease while the latter is associated with aging bone marrow. A substantial proportion of pediatric MDS is caused by germline mutations,

most commonly in GATA2 and SAMD9/SAMD9L. Various aspects and challenges of the diagnosis, surveillance and treatment of children and family members with primary MDS are discussed in detail.

What unites the semi-chronic disease of childhood MDS with pediatric acute leukemias is that all of them are diseases in which the normal development of the hematopoietic system is perturbed. Thus, the primary somatic driving mutations occur already *in utero*. Mutated genomic pathways typically cause differentiation arrest and enhanced self-renewal. Predisposing genetic syndromes often affect the development of other tissues (e.g., deafness and skeletal abnormalities in GATA2 germline syndromes). Furthermore, normal development of various tissues in the growing children is also often affected by chemotherapy, leading to pediatric-specific toxicities. Curing every child with a hematologic malignancy while minimizing these short- and long-term toxicities remains a major challenge.

Disclosures

No conflicts of interest to declare

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