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Refractory ALL Despite the Use of Innovative Therapies

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Background. Innovative therapies offer a cure for relapsed/refractory hematologic malignancies. However, disease biology remains of paramount importance for survival. We aim to present a case of resistant acute lymphoblastic leukemia (ALL) despite the use of innovative approaches.

Case description. The boy was diagnosed with ALL, CNS1 at 3 years of age. The leukemic population expressed a B-precursor phenotype, hyperdiploid karyotype (50XY) without genetic aberrations. The patient was treated according to the NOPHO-ALL-2008 protocol, achieved 1CR, negative MRD (MRD-), and was stratified to the standard risk group. Still on maintenance therapy, the 1st early bone marrow (BM) relapse, CNS2 was diagnosed. Two courses of high-risk chemotherapy failed to achieve remission. Thus, blinatumomab was administered and 2CR/MRD- was documented. The patient was consolidated with allo-HSCT from HLA-identical sibling 2 years and a half after the initial diagnosis. A myeloablative chemotherapy-based conditioning was used prior to PBSC infusion. The post-transplant course was uneventful except for mild chronic GvHD. However, 11 months after HSCT the 2nd BM relapse, CNS2 developed. Relapsed leukemic cells expressed identical diagnostic phenotype, but karyotype turned from hyper- to normoploid (46YX). No genetic aberration was detected either. The patient was referred to Oslo University Hospital where CAR-T cells (CART19, Kymriah©) were infused. The post-infusion toxicity was grade 0-I. Thereafter the 3CR/MRD- was documented, however, continued only for 2 months. Due to increasing MRD the 2nd CAR-T cell dose of the same product was infused, unfortunately with no effect – the 3rd BM relapse was diagnosed in 1 month after the 2nd dose. Two courses of blinatumomab induced the 4CR/MRD-, consolidated with the 2nd allo-HSCT from the same donor after TBI. Despite all efforts increasing MRD was documented 6 months after HSCT, nearly 5 years after initial diagnosis.

Conclusion. A better understanding of ALL biology is needed to overcome resistant disease and offer personalized therapy.