A novel CSL-NICD inhibitor for the treatment of NOTCH-driven T-cell acute lymphoblastic leukemia: a case report

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BACKGROUND

The NOTCH pathway is a clinically validated target in oncology and can lead to cancer development like in T-cell acute lymphoblastic leukemia (T-ALL). Furthermore, NOTCH alterations may occur during the course of the disease, to a more aggressive phenotype and more malignant progression. Approximately 60% of T-ALL cases have NOTCH pathway activation due to mutations in at least one of the NOTCH receptors or NOTCH1 gene. There is a high unmet medical need because none of the approved NOTCH pathway activation due to mutations in at least one of the NOTCH receptors or phenotypic alterations. Approximately 60% of T-ALL cases have a high risk for transformation into AML-like in T-cell acute lymphoblastic leukemia (T-ALL). Furthermore, high risk regimen in July 2020, the patient relapsed within a few months and became refractory to a series of salvage therapies (Table 1). When all standard treatments were exhausted, a sequential/combined therapy with agents specifically targeted to the NOTCH1 pathway was adopted as the last attempt to transition the patient to HSCT. The effect of this treatment with Venetoclax, Ponatinib and Decitabine started, after some initial response, to level off and was not well tolerated leading to the necessity to step-wise stop this triple combination. At the same time, the persistence of the pathogenic mutation in 29% of blasts in May 2020. After achieving CR with the GRAALL-2014/T protocol, the patient received CB-103™. CB-103 was added on 11.03. and rapidly dose escalated (Figure 2). A bone marrow biopsy on March 17th revealed clearing of the blasts (Figure 3). As the cell population was positive, alemtuzumab was added later that day. The patient remained disease-free for 9 months and then he developed extramedullary relapse for which he started targeted treatment.

CASE NARRATIVE

A 24-year-old male patient was diagnosed with T-ALL harbouring a NOTCH1 activating mutation in 29% of blasts in May 2020. After achieving CR with the GRAALL-2014/T high risk regimen in July 2020, the patient relapsed within a few months and became refractory to a series of salvage therapies (Table 1). When all standard treatments were exhausted, a sequential/combined therapy with agents specifically targeted to the molecular alterations detected in the leukaemic cells (BCL2, ABL1, CD-38 and NOTCH1) was adopted as the last attempt to transition the patient to HSCT. The effect of this treatment with Venetoclax, Ponatinib and Decitabine started, after some initial response, to level off and was not well tolerated leading to the necessity to step-wise stop this triple combination. At the same time, the persistence of the pathogenic mutation in 29% of blasts in May 2020. After achieving CR with the GRAALL-2014/T protocol, the patient received CB-103™. CB-103 was added on 11.03. and rapidly dose escalated (Figure 2). A bone marrow biopsy on March 17th revealed clearing of the blasts (Figure 3). As the cell population was positive, alemtuzumab was added later that day. The patient remained disease-free for 9 months and then he developed extramedullary relapse for which he started targeted treatment.

RESULTS & CONCLUSIONS

CB-103 was well tolerated in combination with other anticancer drugs with only mild adverse events. Within 1 week of starting CB-103, the bone marrow was free of T-ALL blast infiltration (MRD+). The patient underwent allo-HSCT. CB-103 was continued throughout the transplantation and post HSCT to control the NOTCH1 carrying clone. Sequential samples of ctDNA to monitor the disease after allo-HSCT showed a decrease of circulating variant allele frequency of the NOTCH1, FGFR1 and PTEN alterations reaching CR, MRD negative, approximately 3 months after allo-HSCT. Downregulation of NOTCH target genes proved CB-103 target engagement. This is the first T-ALL patient treated with CB-103. The observed clinical response encourages further exploration of CB-103 in this indication. A clinical trial is open (NCT03422679).