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abstract

The Innovative Bridge in Ph Positivity- Efficacy and Side Effect Profile of Inotuzomab Ozogamicin and Ponatinib Combination in Relapsed PH-positive and PH-like ALL

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The Innovative Bridge in Ph Positivity- Efficacy and Side Effect Profile of Inotuzomab Ozogamicin and Ponatinib Combination in Relapsed PH-positive and PH-like ALL

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Introduction: Philadelphia (PH) chromosome-positive or PH-like B-Acute lymphoblastic leukaemia has a high risk of relapse, and several drugs have been used to achieve complete remission (CR) before transplant, one of which is a combination of Inotuzumab ozogamicin (INO) and ponatinib. This study aims to evaluate the efficacy and side effects of inotuzumab in combination with ponatinib in this category as a bridge to transplant.

Methodology: The study reports 10 cases of relapsed PH-positive and PH-like B-ALL who received a 21-day regimen of INO 1.5 mg/kg over days 1,8, and 15, along with ponatinib. We studied the timing and type of relapse, use of other salvage chemotherapy before the combination, timing and side effects of the combination with MRD thereafter, and post-HSCT outcome.

Results: Ten children with relapsed B ALL were included, with a mean age of 11.2 years, of which 4 were boys. 7/10 were PH-positive ALL, and 3/10 were PH-like ALL. One had a very early relapse, 8/10 had early relapse, and 1 had late relapse. 4/10 had combined relapse, 5/10 had isolated medullary relapse, and 1/10 had isolated CNS relapse.Timing of INO-ponatinib: 5/10 received the combination post reinduction, 3/10 after FLAG chemotherapy, 1 post Blinatumomab, and 1 post hyper CVID with Nilotinib. All were MRD positive before the combination. CR post the combination was seen in 9/10, and in the remaining 1/10, CR was achieved after cyclophosphamide and cytarabine.

9/10 children underwent post-HSCT, while one child deferred transplant and succumbed. All children post-HSCT are in remission in the 2-year follow-up.

Side effect profile of inotuzumab ozogamicin and ponatinib combination:
Fevern – 4/10
Erythematous maculopapular rash 3/10
Thrombocytopenia < 1000 7/10
Admission for febrile neutropenia 3/10
Body pain 2/10
Sinusoidal Obstruction Syndrome during combination 2/10
Sinusoidal Obstruction Syndrome during transplant 0/10

The development of several tyrosine kinase inhibitors (TKIs) that target the BCR: ABL fusion protein has revolutionized the management of patients with PH-positive ALL. However, Children with Philadelphia chromosome-positive or PH-like B-acute lymphoblastic leukaemia have a high risk of relapse despite the use of upfront TKIs.
To overcome the unfavourable outcome of refractory relapsed PH-positive B-ALL, several drugs have been used to achieve CR before transplant. In Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia, allogeneic hematopoietic cell transplant (allo-HCT) remains the standard strategy for achieving long-term disease-free survival.

Inotuzumab is a humanised CD22 monoclonal antibody. In the INO-VATE trial, patients with relapsed/refractory acute lymphocytic leukemia who received inotuzumab versus standard chemotherapy achieved greater remission and MRD-negativity rates as well as improved overall survival.

Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) often used in combination with other therapies, like blinatumomab therapy, to achieve remission in children with Ph and Ph-like ALL.

While several studies have proved their individual efficacy and both drugs are FDA approved in the treatment of Ph and PH-like ALL, this

study explores the efficacy and side effect profile of the combination in bringing about complete remission prior to transplant in this vulnerable group.

Conclusion: The combination of inotuzumab and ponatinib is cost-effective and well tolerated as an outpatient regimen. It has 80% efficacy in inducing CR with a mild side effect profile, hence a good bridging regimen to transplantation.