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ELEVENTH ANNUAL MEETING

INOTUZUMAB OZOGAMICIN IN THE TREATMENT OF RELAPSED/REFRACTORY (R/R) PH-POSITIVE ACUTE LYMPHOID LEUKEMIA WITH EXTRAMEDULLARY DISEASE - OUR EXPERIENCE

Maria Dragoescu MD[1], Alexandra Ghiaur MD[1], Daniel Coriu PhD, [1,2]
[1]Center of Haematology and Bone Marrow Transplant, Fundeni Clinical Institute, Bucharest, Romania.
[2]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

INTRODUCTION

At disease recurrence, a significant proportion of patients with B-ALL present with extramedullary involvement. Inotuzumab ozogamicin (IO) is a calicheamicin-based antibody-drug conjugate targeting CD22 that is a valuable asset in the management of R/R B-ALL. We present 2 cases of relapsed Ph-positive B-ALL with non-CNS extramedullary disease treated with IO.

CASE 1

Initial workup and diagnosis

Medical history: A previously healthy 32-year-old woman who gave birth to a healthy child just 3 months before, presented in December 2019 with 3 weeks history of severe generalized musculoskeletal pain.

Physical examination revealed a mildly enlarged spleen.

Laboratory findings: Initial blood counts and peripheral blood smear showed leukocytosis (WBC=96 x 10^9/L) with 83% blasts. Biochemistry was within normal ranges, except for an elevated LDH. Bone marrow biopsy and aspirate revealed 90% blasts. Flow cytometry performed on bone marrow sample found a population of 80% blast cells which expresses icCD79a+, CD19+, CD10+, CD22+, CD66c+, CD123+ , compatible with pre-B acute lymphoblastic leukemia. Molecular studies revealed a minor transcript (p190) of the breakpoint cluster region-Abelson (BCR-ABL). Cytogenetic analysis found a corresponding translocation (9;22).

Treatment and disease course

The patient was initially treated with chemotherapy and Imatinib by GRAAPH 2005 Protocol. At the end of induction she achieved morphologic CR, but positive MRD. She developed gastrointestinal intolerance to Imatinib (diarrhea, nausea, vomiting), consequently she was switched to Dasatinib. From January to August 2020, in addition to intrathecal CNS prophylaxis, she received 4 cycles arm A and 4 cycles arm B of Hyper-CVAD plus Dasatinib 100mg/day with morphologic CR and MRD negativity. In september 2020 our patient received HSCT from an HLA-matched unrelated male donor. Chimerism on D30 was 100% donor and Dasatinib was resumed. 3 months after HSCT she experienced medullary relapse with 46% blasts in bone marrow aspirate. The ABL1 T315I mutation was found and she started treatment with ponatinib and steroids, with achievement of minimal residual disease (MRD) negativity both by polymerase chain reaction and flow cytometry. She refused a second HSCT and continued maintenance with ponatinib. Four months after the initial HSCT, she relapsed with extramedullary involvement of the breast and ovaries. She was treated with one course of methotrexate and cytarabine-based chemotherapy, with progressive disease. Therefore, she received 6 cycles of IO with complete metabolic response.

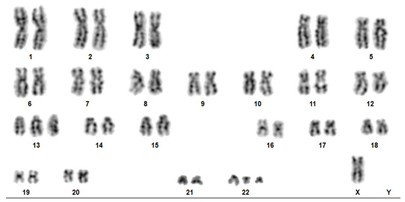


Fig. 1 – Karyotype at diagnosis

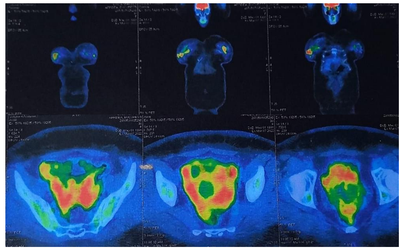


Fig.2 - PET-CT scan (march 2022) – multiple sites of pathological uptake within breasts and ovaries

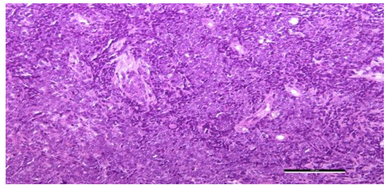


Fig. 3 - Breast biopsy – diffuse blastic infiltration (HE stain, 20x)

CASE 2

Intial workup and history

Medical history: A 23-year-old man presented in May 2020 with intense lower limb pain and vertigo.

Physical examination showed bilaterally enlarged lymphnodes in the cervical and axillary regions and moderate splenomegaly.

Laboratory findings: Initial blood counts and peripheral blood smear showed leukocytosis (WBC= 208 x 10^9/L) with 93% blasts, severe macrocytic anemia (Hb=50 g/L) and severe thrombocytopenia (Plt= 17 x 10^9/L). Biochemistry studies revealed an elevated LDH. Bone marrow aspirate found 94-96% blasts. Flow cytometry was performed on a bone marrow sample and was compatible with common B-ALL. Molecular studies revealed a minor transcript (p190) of the breakpoint cluster region-Abelson (BCR-ABL). Cytogenetic analysis found a corresponding translocation (9;22) in 72% of the cells.

Treatment and disease course

The patient was initially treated by GRAAPH-2005 (with imatinib) protocol with complete remission. Following the remission, he refused HSCT based on personal consideration and received maintenance with imatinib.

He experienced medullary relapse 13 months after the initial diagnosis and the tyrosine kinase inhibitor imatinib was switched to dasatinib.

Under dasatinib, the disease progressed, so the TKI was switched to ponatinib, administered in conjunction with steroids.

He achieved complete response with MRD negativity after 1 cycle of ponatinib+steroids.

After 3 months, he started complaining of intense pain localized in the right hip. A MRI and a CAT scan of the pelvis were performed. Bilaterally multiple lesions randomly distributed in the pelvis and femurs were discovered (largest lesion of 43/80mm). A bone biopsy from the right femoral head was performed. The histopathology examination described a malignant proliferation of the cells which resembled lymphoblasts. In the bone marrow aspirate a proportion of 1.55% atypical lymphoblasts was revealed.

Hence, the patient experienced relapse with extramedullary involvement for which he was treated with 2 cycles of IO with complete metabolic response and agreed to proceed to HSCT.

CONCLUSIONS

These 2 cases underscore the potential benefits of IO in Ph-positive advanced B-ALL with extramedullary involvement in comparison with classical chemotherapy. Although notable adverse events can occur during treatment with this novel agent, it was well tolerated by our patients, with only grade 1 hepatotoxicity by elevated alanine aminotransaminase and aspartate transaminase in our male patient.

CONTACT INFORMATION

fraseniuc.maria@yahoo.com

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