Case Report-III

Prolonged Neutropenia Associated with Rituximab Therapy - A Case Report

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ABSTRACT

Rituximab a monoclonal antibody is effective in CD20 positive B cell lymphoma and is now widely used either as a single agent or in combination with chemotherapy. The antibody toxicity is generally mild and transient. However, there are reports of prolonged and severe neutropenia in patients treated with rituximab. We report a patient with non Hodgkin's lymphoma diffuse large 'B' cell type, stage IIIA who was treated with CHOP chemotherapy combined with rituximab. Six weeks after the initiation of treatment marked neutropenia occurred and persisted for 13 months. Patient developed multiple episodes of febrile neutropenia and required growth factor support in all occasions. Delayed onset neutropenia is a newly recognized toxicity of rituximab treatment which may last up to one year and can be associated with serious infections.

INTRODUCTION

Monoclonal antibody therapy with the anti CD20 antibody rituximab has already had an enormous impact on the treatment of B cell lymphoma and auto immune disorders. The treatment is generally safe and well tolerated and exhibits little interaction with conventional chemotherapies. However, there are some unique toxicities which are newly recognized.

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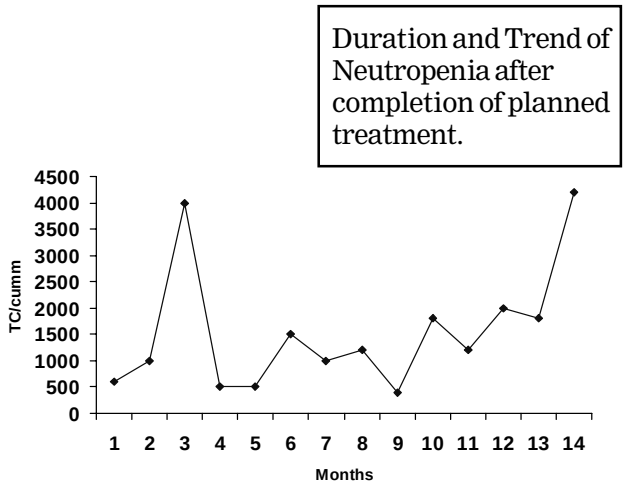
CASE: A 40 year old male was diagnosed with CD20 positive diffuse large B cell type non hodgkins lymphoma stage IIIA. Treatment with CHOP regimen in combination with rituximab for eight courses was initiated. Complete remission of non hodgkins lymphoma was documented by repetitive CT scans and clinical examination. Six weeks after the first cycle of combined chemotherapy and rituximab, severe neutropenia developed and persisted for 13 months. Patient developed eight episodes of grade IV febrile neutropenia and required hospitalization with broad spectrum antibiotics and growth factor support. There was no associated anemia or thrombocytopenia. Bone marrow studies obtained 4 months after the neutropenia disclosed hypocellular marrow with marked reduction in mature neutrophils and neutrophil precursors. Immunoglobulin assays done were normal. Viruses known to cause neutropenia were ruled out by PCR studies. Antibodies bound to the surface of neutrophils were not assessed in our patient. The neutropenia persisted for 13 months required periodic hospitalization and did not respond to G-CSF. The neutropenia of our patient recovered spontaneously. He remains in complete remission 25 months after treatment.

DISCUSSION

It is well known that rituximab reversibly depletes normal B lymphocytes and occasionally leads to hypogamma globulinemia. Recovery is

expected within one year.[1] In the pivotal studies single agent rituximab was associated with delayed onset neutropenia, NCI grade 3 - 4 in up to 8%.[1] In the transplant setting delayed onset neutropenia following rituximab has been observed in 43 - 54%.[2-3] One of the most frequent adverse events during the follow up period after rituximab monotherapy i.e. 30 days after the last infusion to 1year after the first infusion was neutropenia (6%).[4] Serious infections are reported in some series, whereas in others neutropenia did not result in complications.[1,3,5] Neutrophil counts recovered spontaneously or responded to G-CSF and / or intravenous immunoglobulin (IVIG) treatment.[6]

The etiology of prolonged neutropenia is not clear. Several hypotheses have been proposed such as transient production of auto antibodies against neutrophils during immune reconstitution.[3,5,7] A direct effect of rituximab is unlikely since granulocytes and haemopoetic precursor stem cells do not express CD20 and the circulating half life of rituximab is known to last from several days to 1 week.[1]



As exposure to rituximab is increasing world wide prolonged neutropenia is a condition which should be recognized. Treatment with G-CSF or IVIG has been tried and needs further evaluation for the effective management of this unique toxicity.

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