Rituximab-Induced Late Onset Neutropenia: Case Report and Review of Literature

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Summary

Single agent rituximab has the potential to cause delayed and late-onset neutropenia that may vary in severity. In this report, we present a case of patient who was treated for mantle cell lymphoma with rituximab that lead to severe late-onset isolated neutropenia, which resulted in delay and subsequent omission of further rituximab cycles. It is important to be aware of this uncommon adverse event, which can occur long after cessation of rituximab therapy.

Keywords: Rituximab, Late onset neutropenia, Absolute neutrophil count.

Introduction

Drug induced neutropenia is a potentially serious and life-threatening adverse event that may occur secondary to variety of agents. Cytotoxic chemotherapy can cause a predictable, reversible and dose-related decrease in neutrophil count. Isolated neutropenia secondary to other medications tends to be an idiosyncratic reaction either as an immune-mediated reaction or because of direct myeloid cell line damage.Rituximab is an IgG1 chimeric human/mouse, anti-CD20 monoclonal antibody indicated for the treatment of variety of B-cell lymphocytic malignancies, including chronic lymphocytic leukemia, follicular lymphoma, mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma.[1] Mechanism of actions of rituximab may occur by antibody-dependent cellular cyto-toxicity (ADCC), complement-dependent cytotoxicity and direct signaling (apoptosis).[2] Delayed and late-onset serious side effects associated with rituximab may include reactivation of hepatitis B (20-55%), interstitial pneumonitis (5.4%) and progressive multifocal leukoencephalopathy (1-2%).[1] When rituximab was added onto chemotherapy regimens, it was found to be safe and tolerable without adding significant hematological toxicities. Post-marketing studies and case reports have shown that rituximab has the potential to cause delayed and late-onset neutropenia (LON) that may vary in severity.[3-5] We report case of a patient who was treated for MCL with rituximab based chemo-immunotherapy followed by single agentrituximab maintenance every two monthly that led to severe LON before fifth cycle, which resulted in delay and subsequent omission of further maintenance rituximab cycles.

Case Report

A 51-year-old male patient presented to our hospital on 22/09/2017 with history of multiple bilateral cervical lymphadenopathy,since 2 months. His ECOG performance status was one. On detailed history and physical examination multiple, firm, discrete lymphadenopathy was found in bilateral cervical region, rest of the physical examination was normal. Excisional biopsy of cervical node was undertaken, which on histopathological examination showed intermediate to high grade non-Hodgkin lymphoma. On immunohistochemistry examination CD5, CD20 and Cyclin D1 were positive and CD23 was negative, hence a diagnosis of MCL was made. On further staging work up, which included contrast enhanced computerized tomography (CECT) scan of neck, thorax, abdomen and pelvis; MCL stage III, according to Lugano staging system was found.[6] Bone marrow aspiration and trephine bone biopsy was normal. Complete blood count (CBC) and serum biochemistry were normal. Following which patient was administered one cycle of cytoreductive chemotherapy consisting of cyclophosphamide, vincristine and prednisolone; followed by three cycles of rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone (R-CHOP) every 21 days, after checking CBC before each dose of chemotherapy cycle. Patient tolerated all chemotherapy cycles very well, with no delay in any scheduled cycle. Interim CECT scan was done after three cycles, which showed more than partial response, according to response evaluation criteria in solid tumor (RECIST) version 1.1. In view of good response, further three cycles of R-CHOP were administered to the patient. CT scan evaluation after six cycles of R-CHOP showed complete response (according to RECIST v1.1). Subsequently patient was started on maintenance therapy with single agent rituximab every two monthly. Patient tolerated four cycles of single agent rituximab maintenance very well. CBC examination done just before scheduled fifth cycle showed, hemoglobin of 13.9 gm/dl, total leucocyte count (TLC) of 2800/cumm, with absolute neutrophil count (ANC) of 448/cumm, which was confirmed manually, and platelet count of 2.45

Table 1: Serial Complete blood count post fourth cycle of single agent rituximab

Date	Total Leucocyte Count(cells/cumm)	Absolute Neutrophil Count(cells/cumm)	Hemoglobin (gm/dl)	Platelet Count(cells/cumm)
03/08/2018	2800	448	13.9	2,45,000
04/08/2018	2300	500	13.5	2,04,000
06/08/2018	2600	640	13.3	1,70,000
09/08/2018	2400	1200	12.9	2,08,000
13/08/2018	4000	1600	13.4	2,19,000

lakh/cumm. Grade IV neutropenia according to common terminology criteria for adverse events (CTCAE) v5.0 was found. Patient was asymptomatic, with no history of any fever episode, cough, rash, malaise, anorexia or nausea/vomiting. Hence infectious causes or viral fever were not suspected or tested. Vitamin B12 deficiency is usually associated with severe anaemia, yellow skin and variable amount of neurological abnormality. Our patient only had isolated neutropenia with normal haemoglobin and platelet count. And also,the temporal course of neutropenia was correlating with previous rituximab administration. Diagnosis of rituximab-induced LON was made. In view of low ANC, rituximab maintenance was deferred, and serial CBC examinations were done biweekly (Table1). ANC gradually recovered to normal value (>1500) over a period of ten days. Granulocyte colony stimulating factors (G-CSFs) administration for ANC recovery was not required. In view of risk of recurrent, severe and prolonged neutropenia, rituximab re-challenge was not attempted. Patient was explained regarding the nature of adverse event and the option of high dose chemotherapy with autologous hematopoietic stem cell transplantation was discussed. Patient opted for no further treatment.

Review of Literature

Pathophysiology

Neutropenia is defined as having an ANC of less than 1500 cells/cumm and is a common adverse event associated with many cytotoxic chemotherapy agents.[7] In patients receiving cancer treatment regimens containing rituximab with cytotoxic chemotherapy (e.g. anthracycline, alkylating agents), the nadir (lowest value) of the patients neutrophil count is expected to occur 10-14 days following administration of each cycle of treatment. Neutrophil recovery will usually occur in three to four weeks following chemotherapy. Single agent rituximab has been reported to cause neutropenia, but with a delayed and often unpredictable onset. Single agent rituximab associated LON has been defined in the literature as developing at least three to four weeks following the end of rituximab administration despite a complete recovery of ANC following chemotherapy.[8] Rituximab-induced LON may be prolonged and result in very unpredictable recovery time.

The mechanism by which rituximab may induce neutropenia has yet to be fully elucidated, variety of theories exist. Direct toxicity is very unlikely. Several studies suggest that LON could be related to an excess of T-large cell lymphoma(T-LGL) in the bone marrow and peripheral blood which express and secrete large amounts of Fas and Fas ligand leading to apoptosis of mature neutrophils, or to a production of autoantibodies binding to the neutrophil surface during recovery of a new immune repertoire.[9] On the other hand, recent studies suggest that LON is not related to circulating factors but to perturbations of stromal derived factor 1 and B cell activating factors, cytokine, affecting granulopoiesis homeostasis during B cell recovery.[10] This is reinforced in the same study showing the hypo cellularity of the bone marrow at time of LON and absence of anti-neutrophil antibodies in the serum or T-LGL in peripheral blood.[10] The intricate balance of lymphopoiesis and granulopoiesis governed by a complex cytokine balance in the bone marrow environment may be hampered by rituximab, resulting in B-cell lymphopoiesis over granulopoiesis within common developmental niches. A recent study correlated specific polymorphism in the immunoglobulin G Fc receptor FCgammaRIIIa 158 V/F with increased rates of LON. Polymorphism in FCGR3A, a low-affinity receptor capable of binding to the Fc portion of complexed IgG, have been implicated in this process.[11] The presence of this polymorphism may facilitate neutropenia by mediating ADCC on malignant and non-malignant B cells, thus increasing the degree of B-cell depletion.[11]

Incidence and risk factors

The reported incidence of rituximab-induce LON varies within the literature. This adverse drug reaction (ADR) may occur in 8% to 27% of cancer patients treated with single agent rituximab.[12] Single agent rituximab-induced LON occurs a median of 38

to 175 days following the last rituximab dose, with a median duration of 5 to 77 days.[13] Despite the proposed high incidence of this ADR, many of the episodes are self-limiting and without any apparent clinical significance. Multiple studies have evaluated the risk factors for developing rituximab-induced LON. Patients with advanced stages of malignancy and those more than 60 years of age are at greater risk.4 Previous treatment with purine analogs or methotrexate and prior autologous peripheral blood stem cell transplantation may also be risk factors for developing rituximab-induced LON.

Management

Most cases of rituximab-induced LON, are, grade 1–2 which are self-limiting and resolve without any complications. However,in grade 3 or 4 neutropenia, there is a potential for prolonged andserious life-threatening infectious complications.[14,15] The delayed onset, unpredictable occurrence and neutrophil recovery associated with single agent rituximab-induced LON can create a clinical challenge for practitioners. Infectious complications, such as neutropenic fever, that may occur because of severe and prolonged neutropenia secondary to rituximab treatment should be managed with antimicrobial therapy. Antimicrobials should be selected and modified based on guideline recommendations.[7] Granulocyte -colony stimulating factors (G-CSFs) can also be used in patients with neutropenic fever with additional risk factors for severe complications, such as those with an ANC of less than 100 cells/cumm and/or with pneumonia, hypotension, multi-organ failure, or invasive fungal infections.[16] G-CSFs are especially useful in managing patients treated with rituximab because they address the unpredictable nature of neutrophil recovery and possible prolonged neutropenic duration. No specific recommendations regarding the optimal ANC target, frequency, and duration of administration of filgrastim products have been proposed to manage this adverse event. The drug is typically administered once daily until neutrophil recovery when it is utilized for neutropenia prophylaxis in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy.[17] Although rituximab-induced LON has the potential to be a long-lasting complication, neutrophil recovery with the use of a filgrastimproduct can occur in as few as four days.7 To keep a patient's ANC greater than 1,000 cells/cumm, maintenance strategies using the drug once or twice weekly may be employed for several months for patients with prolonged neutropenia despite initial neutrophil recovery.[3] Given the unclear nature and mechanism of rituximab-induced LON, it is not fully known and understood if re-treatment with rituximab is a viable and safe option for patients. It has been previously reported that re-challenging a patient with rituximab following an episode of severe LON can lead to recurrent episodes.[13] With the possibility of recurrence and the unclear risks and implications of retreatment, the decision to administer further doses of rituximab should be made on a case-by-case basis. Future research is needed in this area.

Conclusion

Single agent rituximab can cause delayed and LON that may last for an unpredictable amount of time. Although most cases appear to be self-limiting and resolve without issue, rituximab-induced LON may result in serious life-threatening complications requiring immediate medical intervention. Diligent patient follow-up is needed to monitor for this adverse event, which may occur long after therapy cessation and therapeutic intervention may be necessary in severe cases that may result in neutropenic fever. This adverse event can pose challenge for clinicians and requires close patient follow-up with CBC monitoring during rituximab administration as well as after therapy has ended.

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