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# Chemotherapy Induced Neutropenia: A Case Series

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**Abstract:** Cytotoxic chemotherapy suppresses the hematopoietic system, impairing host protective mechanisms and limiting the doses of chemotherapy that can be tolerated. Neutropenia, the most serious hematologic toxicity, is associated with the risk of life-threatening infections as well as chemotherapy dose reductions and delays that may compromise treatment outcomes. Chemotherapy induced late onset neutropenia, despite its importance as the primary dose-limiting toxicity, much concerning neutropenia and its consequences and impact remains unknown. Recent surveys indicate that neutropenia remains a prevalent problem associated with substantial morbidity, mortality and costs. Rituximab can cause late-onset neutropenia that may result in serious life-threatening complications. Much research has sought to identify risk factors that may predispose patients to neutropenic complications, including febrile neutropenia, in an effort to predict better which patients are at risk and to use preventive strategies, such as prophylactic colony-stimulating factors, more cost-effectively. Neutropenic complications associated with myelosuppressive chemotherapy are a significant cause of morbidity and mortality, possibly compromised treatment outcomes and excess healthcare costs. Research in quantifying the risk of neutropenic complications may make it possible in the near future to target patients at greater risk with appropriate preventive strategies, thereby maximizing the benefits and minimizing the costs.

**Keywords:** Chemotherapy Induced Neutropenia (CIN), Risk Factors, Rituximab induced late-onset neutropenia, Colony-Stimulating Factors.

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**INTRODUCTION:** Cytotoxic chemotherapy predictably suppresses the hematopoietic system, impairing host protective mechanisms. Neutropenia is the most serious hematologic toxicity of cancer chemotherapy, often limiting the doses of chemotherapy that can be tolerated. The degree and duration of the neutropenia determine the risk of infection.[1, 2]

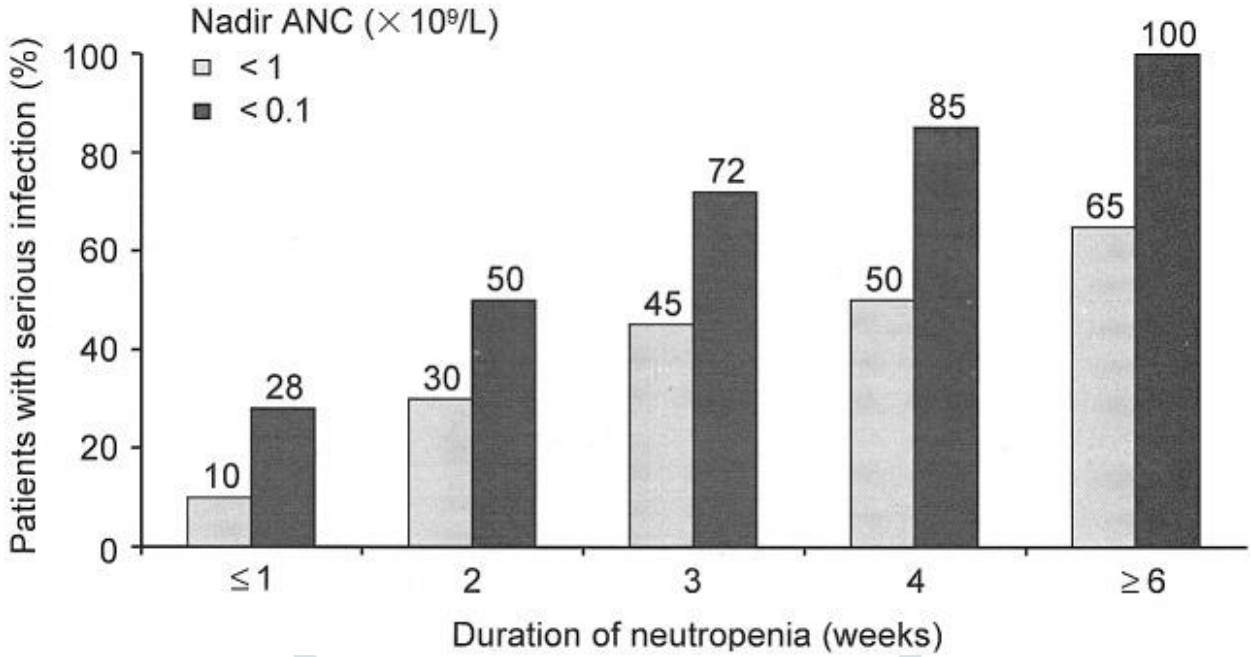


**FIGURE 1 Incidence of serious infection, by nadir absolute neutrophil count (ANC) and duration of neutropenia.[1]**

The Common Toxicity Criteria of the National Cancer Institute is the most commonly used scale for grading the severity of the cytopenia's associated with cancer chemotherapy; it delineates neutropenia into 4 grades.[3]

**TABLE 1 Grades of Neutropenia[a]**

| Grade | Absolute neutrophil count (x$10^9$/L) |
|---|---|
| **0** | Within normal limits |
| **1** | ≥ 1.5 to < 2.0 |
| **2** | ≥ 1.0 to < 1.5 |
| **3** | ≥ 0.5 to < 1.0 |
| **4** | < 0.5 |

[a]According to the National Cancer Institute Common Toxicity Criteria, version 2.0.3

Drug-induced neutropenia (CIN) is a potentially serious and life-threatening adverse event that may occur secondary to therapy with a variety of agents. Cytotoxic chemotherapy can cause a predictable and dose-related decrease in neutrophil count. 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. This effect has been associated with a variety of medications including, but not limited to, Clozapine, Dapsone, Methimazole, Penicillin, Rituximab and Procainamide.[4] For a comprehensive list of medications associated with the development of neutropenia, are as;

**Medications Associated with the development of Neutropenia**[4, 5]

**Non-chemotherapy** – Clozapine, Dapsone, Hydroxychloroquine, Infliximab, Lamotrigine, Methimazole, Oxacillin, Penicillin G, Procainamide, Propylthiouracil, Quinidine/Quinine, Rituximab, Sulfasalazine, Trimethoprim/sulfamethoxazole and Vancomycin.

**Chemotherapy -** Alkylating agents, Anthracyclines, Antimetabolites, Camptothecins, Epipodophyllotoxins, Hydroxyurea, Mitomycin C, Taxanes and Vinblastine.

Neutropenia from nonchemotherapy drugs is much less common than neutropenia secondary to chemotherapy.[5] Rituximab is an anti-CD20 mono clonal antibody indicated for the treatment of a variety of B-cell lymphocytic malignancies, including chronic lymphocytic leukaemia (CLL), follicular lymphoma and diffuse large B-cell lymphoma.[6] Rituximab is also used for the management of several autoimmune disorders, such as Rheumatoid arthritis (RA) and Wegener's granulomatosis. In the treatment of B-cell malignancies, this monoclonal antibody exerts its anticancer activity by depleting malignant B cells via mechanisms such as complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and by inducing apoptosis.[7] In the treatment of cancer, Rituximab can be administered as monotherapy or in combination with chemotherapy agents, depending on the indication.

Common adverse events associated with Rituximab therapy include acute infusion reactions, lymphopenia, infection and asthenia.[6] Delayed and late-onset serious side effects may include progressive multifocal leukoencephalopathy, reactivation of hepatitis-B and interstitial pneumonitis. When Rituximab was added onto chemo therapy 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 that may vary in severity.[8 - 10] We report 2 cases, who were treated for hematological malignancies with Rituximab that led to severe, late-onset neutropenia resulting in neutropenic fever, which required hospitalization.

**PATHOPHYSIOLOGY:** Neutropenia is defined as having an absolute neutrophil count (ANC) of less than 500 cells/mm$^3$ and is a common adverse event associated with many cytotoxic chemotherapy agents.[11] During cytotoxic chemotherapy, neutropenia typically occurs during the nadir - the lowest value to which the neutrophil count will fall following drug administration. The nadir typically occurs 10 - 14 days following chemotherapy administration during each treatment cycle. Neutrophil recovery will usually occur in 3 - 4 weeks following treatment. Exceptions to this include agents such as Mitomycin, Carmustine and Lomustine, which have a delayed nadir of about 4 - 6 weeks following administration of each cycle. During treatment with these agents, neutrophil recovery will usually occur 6 - 8 weeks following treatment. The nadir and neutropenia associated with most types of cytotoxic chemotherapy are considered to be rather predictable in onset and occurrence.

In patients receiving cancer treatment regimens containing Rituximab with cytotoxic chemotherapy (Eg; anthracyclines, purine antagonists, alkylating agents etc.), the nadir of the patient's neutrophil count is expected to occur 10 - 14 days following administration of each cycle of treatment. Rituximab has been reported to cause neutropenia, but with a delayed and often unpredictable onset. Rituximab associated late-onset neutropenia has been defined in the literature as neutropenia developing at least 3 - 4 weeks following the end of Rituximab administration despite a complete recovery of ANC following chemotherapy.[12] It has also been reported that

Rituximab may induce neutropenia more than 40 days after the end of treatment.[13] Neutropenia with cytotoxic chemotherapy recovers with a very predictable pattern and is typically short-lived in duration; however, Rituximab induced late-onset neutropenia may be prolonged and result in a very unpredictable recovery time. Without the utilization of granulocyte-colony stimulating factors (GCSFs), Rituximab induced late-onset neutropenia may last a median of 6 - 77 days.[14]

Most cases of Rituximab induced late-onset grade 1–3 neutropenia is self-limiting and resolve without any complications. However, there is the possibility of more severe cases in grade 4 neutropenia.[13, 15] In grade 3 or 4 neutropenia, there is a potential for prolonged and serious life-threatening infectious complications. The delayed onset, unpredictable occurrence and neutrophil recovery associated with Rituximab induced late-onset neutropenia can create a clinical challenge for practitioners. Diligent patient follow-up is needed to monitor for this adverse event and therapeutic intervention may be necessary in severe cases that may result in neutropenic fever. **Mechanism of Adverse Drug Reaction (ADR):** Most cytotoxic chemotherapy exerts its pharmacological activity by causing DNA damage in either a cell-specific or cell-nonspecific manner. By damaging the DNA of malignant cells, chemotherapy is able to produce killer malignant cells. Many chemotherapy agents cause bone marrow suppression resulting in neutropenia, which leads to an increased risk of infection. The mechanism by which Rituximab may induce neutropenia has yet to be fully elucidated; however, a variety of theories exist.

After Rituximab administration, antibodies against neutrophils may be produced, resulting in neutropenia.[16] It may also develop due to aberrant B-cell reconstitution after Rituximab administration. Another theory is that homeostasis of granulocytes may be disturbed by chemokine stromal-derived factor-1 interacting with B-lymphocyte recovery. One of the most compelling theories is that it may occur due to polymorphisms in the immunoglobulin G (IgG) Fc receptor (FcγR). Patients harboring the FcγRIIIa 158 V/F polymorphism were found to have a higher incidence of Rituximab induced neutropenia.[17] The presence of this polymorphism may facilitate neutropenia following Rituximab administration by mediating antibody-dependent cell-mediated cytotoxicity on malignant and non-malignant B cells, thus increasing the degree of B-cell depletion.

**Incidence and Risk Factors:** The reported incidence of Rituximab induced late-onset neutropenia varies within the literature. This ADR may occur in 8 - 27% of cancer patients treated with Rituximab.[18] The incidence of Rituximab induced late-onset neutropenia has been reported to be much lower in patients being managed with Rituximab for autoimmune disease. These rates are as low as 1.3 - 2.3%.[19] Despite the proposed high incidence of this ADR, many of the episodes are self-limiting and without any apparent clinical significance. In rare cases, severe neutropenia has the potential to occur, which can place patients at risk for life-threatening infectious complications. Severe neutropenia resulting in neutropenic fever and infection can lead to hospitalization, the need for broad-spectrum antibiotics and the potential sequelae of bacteraemia and it can be fatal.

Multiple studies have evaluated the risk factors for developing Rituximab induced late-onset neutropenia. Patients with advanced stages of malignancy and those more than 60 years of age are at greater risk.[9, 12] Previous treatment with purine analogs or Methotrexate and prior autologous peripheral blood stem cell transplantation may also be risk factors for developing Rituximab induced late-onset neutropenia. In addition, patients harboring the IgG Fcγ RIIIa 158 V/F polymorphism are at high risk for developing this ADR.[15,17] In patients receiving Rituximab for non-cancer indications, age and female gender have been found to increase the risk for this adverse event.[19]

**Management:** 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.[11] Empiric treatment of neutropenic fever usually includes an antipseudomonal beta-lactam, such as Cefepime, Ceftazidime, Piperacillin-Tazobactam, Meropenem or Imipenem. Treatment against methicillin-resistant Staphylococcus aureus (MRSA) with agents such as Vancomycin should be included in empiric antimicrobial regimens when other additional clinical indicators are present, such as pneumonia, skin or soft tissue infection or suspected catheter-related infection or if the patient is hemodynamically unstable. GCSFs 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/$mm^3$ and/or with pneumonia, hypotension, multiorgan failure or invasive fungal infections.[20] GCSFs, such as Neupogen, Granix and Zarxio, stimulate and promote the maturation and activation of neutrophils. This class of drugs can also enhance the exodus of mature neutrophils trapped within the bone marrow. Through these mechanisms, GCSFs have demonstrated proven efficacy in their ability to reduce the incidence, magnitude and duration of neutropenia following chemotherapy administration.

In severe cases of Rituximab induced late-onset neutropenia, especially with infectious complications, the utilization of filgrastim or a filgrastim biosimilar may be warranted. Filgrastim products 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.[21] Although Rituximab induced late-onset neutropenia has the potential to be a long-lasting complication, neutrophil recovery with the use of a filgrastim product can occur in as few as four days.[12] To keep a patient's ANC greater than 1,000 cells/$mm^3$, maintenance strategies using the drug once or twice weekly may be employed for several months for patients with prolonged neutropenia despite initial neutrophil recovery.[8]

**Case 1:** A 82-year-old woman with a history of stage IVA small lymphocytic lymphoma (SLL) presented to the emergency department (ED) with complaints of fatigue and fever. 42 - days prior to presentation, her SLL was treated with Bendamustine 189 mg (90 mg/$m^2$) on days 1 and 2 and Rituximab 788 mg (375 mg/$m^2$) on day 1 of a 28-day cycle. Subsequently, her treatment was temporarily held due to severe thrombocytopenia secondary to Bendamustine; she was scheduled to resume treatment with a reduced dose of Bendamustine within 2 days of presentation to the ED. Her past medical history was also significant for Peripheral Vascular Disease (PVD), Coronary Artery Disease (CAD), Hypertension (HTN) and chronic kidney disease (CKD). Her home medication list included Aspirin 75 mg daily, Clopidogrel 75 mg daily, Atorvastatin 40 mg daily, Carvedilol 3.125 mg twice daily, Hydrochlorothiazide 12.5 mg daily, Losartan 25 mg daily and a Multivitamin.

**Table 2 Patient Laboratory Values**

| Tests and Vital Signs (normal range) | Hospitalization Day | | | |
|---|---|---|---|---|
| | Day 1 | Day 2 | Day 3 | Day 4 |
| WBC x $10^3$ cells/$mm^3$ (3.5 – 11 x $10^3$ cells/$mm^3$) | 0.9 | 2.8 | 4.9 | 7.9 |
| ANC, cells/$mm^3$ (> 1,500 cells/$mm^3$) | 467 | 1876 | N/A | 6123 |
| Hemoglobin, g/dL (13.3 – 17.7 g/dL) | 09 | 08 | 7.9 | 7.9 |
| Haematocrit, % (40 – 52 %) | 26.5 | 27.9 | 23.3 | 21.9 |
| Platelets x 109/L (150 – 400 x $10^9$/L) | 119 | 92 | 98 | 108 |
| Blood pressure, mm Hg (90 – 149/60 – 90 mm Hg) | 129/49 | 139/79 | 149/69 | 119/56 |
| Pulse, bpm (60 –120 bpm) | 117 | 95 | 77 | 69 |
| $T_{max}$°F (97.8 – 99) | 103.8 | 101.2 | 100 | 99.5 |

Her ANC was 467 cells/mcL (neutropenic). The patient had not demonstrated neutropenia from the time of her diagnosis until her ED presentation. On presentation, the patient had a maximum body temperature ($T_{max}$) of 103.8°F, a blood pressure of 129/49 mm Hg and a heart rate of 117 beats/minute. She was admitted for empirical treatment and management of neutropenic fever and was initiated on Cefepime 2 g intravenously (IV) every 8 - hours and tbo-filgrastim 480 mcg subcutaneously once daily. Blood cultures showed Pseudomonas aeruginosa that was sensitive to Ciprofloxacin, Cefepime, Piperacillin-tazobactam and Meropenem. Cefepime was continued for the duration of her $4^{th}$ day hospitalization and he was discharged on oral Ciprofloxacin to complete his antibiotic course. Filgrastim was continued for a total of 3 doses. On hospital day 2, neutrophil recovery was evident with his ANC rising to 1,876 cells/mcL. Upon further follow-up, no active antineoplastic regimens were subsequently utilized and laboratory tests revealed no further episodes of neutropenia.

**Case 2:** A 77-year-old woman with a long history of CLL presented to the ED with complaints of fever and right foot pain. Her CLL had been under observation for 17 years, but 5 - months prior to presentation, she began treatment for CLL secondary to new-onset autoimmune haemolytic anemia and thrombocytopenia. She received 4 - cycles of Bendamustine 157 mg (90 mg/$m^2$) on days 1 and 2 and Rituximab 653 mg (375 mg/$m^2$) on day 1 every 28 days. When she was evaluated for a $5^{th}$ chemotherapy cycle about a month before her ED presentation, neutropenia was identified and her treatment was discontinued. Her past medical history was also significant for HTN, Type II diabetes mellitus (DM) and gastroesophageal reflux disease (GERD). Her home medications included Lisinopril 20 mg daily, Hydrochlorothiazide 25 mg daily and Pantoprazole 40 mg daily.

**Table 3 Patient Laboratory Values**

| Tests and Vital Signs (normal range) | Hospitalization Day | | | |
|---|---|---|---|---|
| | Day 1 | Day 2 | Day 3 | Day 4 |
| WBC x $10^3$ cells/$mm^3$ (3.5 – 11 x $10^3$ cells/$mm^3$) | 0.7 | 2.3 | 2.9 | 3.7 |
| ANC, cells/$mm^3$ (> 1,500 cells/$mm^3$) | 238 | 558 | 998 | 6569 |
| Hemoglobin, g/dL (13.3 – 17.7 g/dL) | 9.8 | 8.9 | 9.3 | 8.9 |
| Haematocrit, % (40 – 52 %) | 27.5 | 26.9 | 26.3 | 24.9 |
| Platelets x 109/L (150 – 400 x $10^9$/L) | 134 | 86 | 95 | 107 |
| Blood pressure, mm Hg (90 – 149/60 – 90 mm Hg) | 109/69 | 139/69 | 141/79 | 121/65 |
| Pulse, bpm (60 –120 bpm) | 110 | 88 | 85 | 89 |
| $T_{max}$°F (97.8 – 99) | 103.8 | 98.2 | 98.6 | 99.5 |

Her ANC was 238 cells/mcL (neutropenic). On presentation, the patient had a $T_{max}$ of 103°F, a blood pressure of 109/69 mm Hg, and a heart rate of 110 beats/minute. She was admitted for empirical treatment and management

of neutropenic fever. Cefepime 2 g IV piggyback (IVPB) every 8 hours was initiated, along with Vancomycin 1.5 g IVPB every 12 hours. She also received Filgrastim 480 mcg subcutaneously once daily. Vancomycin was empirically started because of a suspected skin and soft-tissue infection on her right foot. Blood cultures were negative. Podiatry was consulted for the foot ulcer, for which an incision and drainage were performed. Cultures of the ulcer grew Pasteurella canis and antibiotics were de-escalated to oral Ciprofloxacin 500 mg twice daily for 10 days. Tbo-filgrastim 480 mcg was administered subcutaneously daily for a total of 3 days. Neutrophil recovery to an ANC of 6,569 cells/mcL occurred on the final day of administration. The patient was discharged after a 4-day hospitalization. Follow-up laboratory tests did not reveal any further episodes of neutropenia.

**CONCLUSION:** Rituximab can cause a delayed and late-onset neutropenia that may last for an unpredictable amount of time. Although most cases appear to be self-limiting and resolve without issue, Rituximab induced late-onset neutropenia may result in serious life-threatening complications requiring immediate medical intervention. When patients with autoimmune disease or cancer are treated with Rituximab, it is important to be aware of Rituximab induced neutropenia, which can occur long after therapy cessation. This adverse event can pose a challenge for clinicians and requires close patient follow-up during Rituximab administration as well as after therapy has ended. Compared with what is reported in the literature, our patients presented in a very similar fashion, given the delayed onset of the neutropenia and the swift ANC recovery following the administration of a filgrastim product. Given the unclear nature and mechanism of Rituximab induced late-onset neutropenia, 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 rechallenging a patient with Rituximab following an episode of severe late-onset neutropenia can lead to recurrent episodes.[22] With the possibility of recurrence and the unclear risks and implications of re-treatment, the decision to administer further doses of Rituximab should be made on a case-by-case basis. So, future research is needed in this area of chemotherapy.

**References:**

1. Bodey GP, Buckley M, Sathe YS, Freireich EJ, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia, Annals of Internal Medicine 1966; 64: 328 – 340.

2. Blackwell S, Crawford J, Filgrastim (r-metHuG-CSF) in the chemotherapy setting. In: Morstyn G, Dexter TM, Foote M, editors, Filgrastim (r-metHuG-CSF) in clinical practice, New York: Marcel Dekker, 1994: 103 – 106.

3. National Cancer Institute, Common toxicity criteria, version 2.0. Available from URL: http://ctep.cancer.gov/forms/ CTCv20_4-30-992.pdf [access date January 3, 2003].

4. Andersohn F, Konzen C, Garbe E, Systematic review: agranulocytosis induced by nonchemotherapy drugs, Annals of Internal Medicine 2007; 146: 657 – 665.

5. Kaufman DW, Kelly JP, Issaagrisil S, *et al.,* Relative incidence of agranulocytosis and aplastic anemia, American Journal of Haematology 2006; 81: 65 – 67.

6. Rituxan (Rituximab) prescribing information, South San Francisco, California: Genentech Inc; March 2016.

7. Johnson P, Glennie M, The mechanisms of action of Rituximab in the elimination of tumor cells, Seminars in Oncology 2003; 30 (1 supply 2): S3 – S8.

8. Motl SE, Baskin RC, Delayed-onset grade 4 neutropenia associated with Rituximab therapy in a patient with lymphoma: case report and literature review, Pharmacotherapy 2005; 25 (8): 1151 – 1155.

9. Nitta E, Izutsu K, Sato T, *et al.,* A high incidence of late-onset neutropenia following Rituximab-containing chemotherapy as a primary treatment of CD20-positive B-cell lymphoma: a single-institution study, Annals of Oncology 2007; 18 (2): 364 – 369.

10. Hirayama Y, Kohda K, Konuma Y, *et al.,* Late onset neutropenia and immunoglobulin suppression of the patients with malignant lymphoma following autologous stem cell transplantation with Rituximab, Internal Medicine Journal 2009; 48 (1): 57 – 60.

11. National Cancer Institute, NCI common terminology criteria for adverse events, v4.0 (CTCAE), May 28, 2009.

12. Friefield AG, Bow EJ, Sepkowitz KA, *et al.,* Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer, Clinical Infectious Diseases 2011; 52: e56 – e93.

13. Arai Y, Yamashita K, Mizugishi K, *et al.,* Risk factors for late-onset neutropenia after Rituximab treatment of B-cell lymphoma. Haematology 2015; 20 (4):196 – 202.

14. Fukuno K, Tsurumi H, Ando N, *et al.,* Late-onset neutropenia in patients treated with Rituximab for non-Hodgkin's lymphoma, International Journal of Haematology 2006; 84: 242 – 247.

15. Tesfa D, Palblad J, Late-onset neutropenia following Rituximab therapy; incidence, clinical features and possible mechanisms, Expert Revision Haematology 2011; 4 (6): 619 – 625.

16. Smith TJ, Khatcheressian J, Lyman GH, *et al.,* 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline, Journal of Clinical Oncology 2006; 24: 1 – 19.

17. Weng WK, Negrin RS, Lavori P, Horning SJ, Immunoglobulin G Fc receptor Fcγ RIIIa 158 V/F polymorphism correlates with Rituximab induced neutropenia after autologous transplantation in patients with non-Hodgkin's lymphoma, Journal of Clinical Oncology 2010; 28 (2): 279 – 284.

18. Grant C, Wilson WH, Dunleavy K, Neutropenia associated with rituximab therapy, Current Opinion Haematology 2011; 18 (1): 49.

19. Salmon JH, Cacoub P, Combe B, *et al.,* Late-onset neutropenia after treatment with Rituximab for Rheumatoid arthritis and other autoimmune diseases: data from the Autoimmunity and Rituximab Registry, Rheumatic Musculoskeletal Diseases Open 2015; 1 (1): e000034.

20. Dunleavy K, Tay K, Wilson WH, Rituximab-associated neutropenia, Semin Haematology 2010; 47 (2): 180 – 186.

21. Neupogen (filgrastim) prescribing information, Thousand Oaks, California: Amgen; July 2015. 22. Wolach O, Bairey O, Lahav M, Late-onset Neutropenia after Rituximab treatment, Medicine 2010; 89 (5): 308 – 318.