Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i1.4105

SEVERITY OF NEUTROPENIA IN PATIENTS WITH NON-HODGKIN B-CELL LYMPHOMAS ON R-CHOP CHEMOTHERAPY REGIMEN

Assam Ahmad[1], Bilal Ahmad[2]*, Syeda Sama bilal[3], Jahan Sardar[4], Sohail Ahmad[5], Rahimullah khattak[6]

[1]Registrar medical oncology unit Allied hospital Abbottabad
[2]*Senior Registrar Oncology Kuwait teaching hospital Peshawar
[3]Medical Officer Health Department KPK
[4]AP medicine Kuwait teaching hospital Peshawar
[5]Specialist Registrar Oncology Hayatabad medical complex Peshawar
[6]AP Medical Oncology Hayatabad Medical Complex Peshawar

***Corresponding Author:** Bilal Ahmad
*Senior Registrar Oncology Kuwait teaching hospital Peshawar
Email: Bilalwazirkmc@gmail.com

Abstract:
Background: Neutropenia is a condition in which the neutrophil concentration in the blood is unusually low. A reduction in the non-marginal pool's circulating neutrophils is known as neutrtropenia. Drug-induced neutropenia affects one person in a million per year, according to the CDC. Non- Hodgkin's lymphoma (NHL) is the category of lymphoproliferative diseases with various clinical and histological presentations.
Objective: To assess the frequency of neutropenia and its severity in patients diagnosed with B-cell Non-Hodgkin's lymphomas on R-CHOP chemotherapy regimen
Material & Methods
Study Design: Cross - sectional study
Study place: Department of Oncology, Combined Military Hospital, Rawalpindi
Duration: 06 months i.e. from 20-5-2019 to 20-11-2019
Data collection: After meeting the inclusion criteria 90 patients were enrolled in this study. Then patients were planned for the first session of RCHOP chemotherapy. The dose of chemotherapy was estimated by using body surface area as per standard guidelines given in operational definition. 48 hours after completion of first cycle of RCHOP therapy, blood CP was performed from the hospital laboratory and neutrophil count along with hemoglobin level was observed. Grade of neutropenia was assessed as per operational definitions.
Results: The mean age of patients was 43.43±11.73 years, 53 (58.89%) were male. Zero grade of anemia was noted in 38 (42.2%) patients. Out of 90 patients, neutropenia was noted in 45 (50%) patients.
Conclusion: Approximately half of the total patients developed neutropenia who were diagnosed with B-cell NHL on R-CHOP chemotherapy regimen

Keywords: Non-Hodgkin's lymphomas, Chemotherapy, Neutropenia

INTRODUCTION:

Non- Hodgkin's lymphoma (NHL) is varied category of lymphoproliferative diseases with various clinical and histological presentations. NHL is predicted to have caused 385,700 new instances of cancer in 2012, and 199,700 people died as a result.1, 2 NHL is the 4th most prevalent cancer among Pakistani men, making up 6.1% of all malignancies.3 It is common practise to provide R-CHOP (Rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy to patients with these conditions in accordance with guidelines provided by the National Comprehensive Cancer Network.4, 5 The "diffuse large B-cell lymphoma" is the most prevalent lymphoid cancer in adults, accounting for 30-40 percent of all NHL cases worldwide.6 Large cells with nuclei at least two times the size of a tiny lymphocyte and generally larger than tissue macrophages make up a diverse category of cancers known as lymphomas.7

Immunohistochemistry reveals the presence of B cell antigens (CD19, CD20, CD22, and CD79a) as well as CD45 on tumour cells in diffuse large B-cell lymphoma that develops from mature B cells resembling centroblasts or immunoblasts in the body.8 Cryoablative chemotherapy has long been the treatment of choice for B-cell lymphomas. 9 CD 20 positive B-cell NHL is now treated with rituximab (a monoclonal antibody to CD20). 10, 11 Neutropenia is the most severe hematologic side effect of chemotherapy including myelotoxic drugs and a major reason why the chemotherapy dosage intensity is not maintained to the target level.12 Having chemotherapy-induced neutropenia increases the risk of serious infections because it dampens the inflammatory response, which allows germs to multiply and infiltrate more easily.13 Despite the fact that overall and event-free survival has improved with the introduction of rituximab, severe side effects such neutropenia remain a problem. Patients treated with CHOP+R treatment have a neutropenia rate ranging from 7% to 65%.14

In a recent study, Yokoyama et al., reported that the incidence of neutropenia after the first cycle was observed in 9.1% (n=42) of B-NHL patients who were on R-CHOP regimen. All of the patients were fall in Grade-IV (very severe) neutropenia with absolute neutrophil count (ANC) <0.5 x 109/L. They further evaluated that neutropenia was more prevalent in the patients with age >65 years (73.8%), female gender (59.5%), hemoglobin level <12g/dL (52.4%) and serum albumin >35 g/L (61.9%), ($P<0.05$).15

Despite the high incidence of neutropenia and its recognized consequences in B-NHL patients undergoing R-CHOP therapy,13-15 very little research has been conducted that investigated its burden and impact in our local population. Complications due to neutropenia may impact the dose regimen, total length of hospitalization and increase the mortality rate due to infections in these patients. If present study results showed remarkably high incidence of neutropenia after R-CHOP therapy in our population, more stringent monitoring with addition of prophylactic treatment like colony stimulating factor may be recommended. This would eventually reduce the overall morbidity and mortality associated with neutropenia in patients receiving R-CHOP therapy for B-cell NHL.

OBJECTIVE: To assess the frequency of neutropenia and its severity in patients diagnosed with B-cell Non-Hodgkin's lymphomas on R-CHOP chemotherapy regimen

MATERIALS AND METHODS:

Study Design: Cross -- sectional study.
Study place: Department of Oncology, Combined Military Hospital, Rawalpindi
Study period: Six months i.e. 20-5-2019 to 20-11-2019
Sample Size: Sample size was calculated by using WHO sample size calculator for estimating a population proportion with specified absolute precision taking Confidence level: 95%, Anticipated population proportion: 9.1%, Precision required: 6%, the sample size calculated comes out to be n=89
Sample Technique: Non -- probability, Consecutive sampling

Sample selection:
Patients of age 15-70 years, both genders, clinically diagnosed cases of B-NHL receiving their first cycle of RCHOP therapy were enrolled. Neutropenia was defined as absolute neutrophils count of <1.9x109/L. It was estimated 48 hours after start of first cycle of R-CHOP chemotherapy regimen. Severity was graded on the basis of neutrophils count from I to IV where I (mild), IT (moderate), III (severe) and IV (very severe) as follows:
Grade-I: 1.5x109/L-1.9x109/L
Grade-IT: = 1.0x109/L-1.4x109/L
Grade-IIT: — 0.5x109/L-0.9x109/L
Grade-IV: <0.5x109/L
R-CHOP Chemotherapy is the chemotherapy regimen comprises of Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone. The regimen shall be administered to the patients diagnosed with B-NHL. The first cycle of chemotherapy was in a dose of Rituximab 375 mg/m2, Cyclophosphamide 750 mg/m2, Doxorubicin 50 mg/m2 and Vincristine 1.4 mg/m2 on day | via the slow intravenous route while Prednisolone was given orally in a dose of 100 mg/day for 5 days.
Patients who previously received any other regimen of chemotherapy, cardiac ejection fraction < 50%, history of diabetes mellitus, baseline neutrophils counts of <1.5x 109/L-1.9x 109/L and already taking steroids were excluded from the study.

Data Collection Procedure: Permission and approval was sought from the hospital ethics committee before conducting the study. Clinically diagnosed patients with B-NHL who are receiving RCHOP therapy, fulfilling the inclusion criteria was enrolled from the indoor/outdoor. Informed written consent was taken from all the patients. A detailed clinical history was taken and thorough physical examination of was performed for all the patients by the trainee researcher himself Base line investigations including complete blood cell counts, glycemic level, uric acid level, renal and liver function tests, plain radiography, ultrasound or CT scan, electrocardiography and echocardiography was done. Then patients underwent first session of RCHOP chemotherapy. The dose of chemotherapy was estimated by using body surface area as per standard guidelines given in operational definition. 48 hours after completion of first cycle of RCHOP therapy, blood profile was performed from the hospital laboratory and neutrophil count along with hemoglobin level was observed. Grade of neutropenia was assessed. All the Study procedures were done by researcher to conserve the quality of the data and compliance to the study protocol. All the collected data and study results were recorded in proforma.

Data analysis: Collected data was entered & analyzed on computer software IBM-SPSS version 22. Numeric variables like age, BMI, and baseline absolute neutrophils count was measured as mean + standard deviation. Categorical variables like Gender, neutropenia and grades of neutropenia was measured as frequency and percentages.

RESULTS:
The mean age of the patients was 43.43±11.73 years. Out of 90 patients 53(58.89%) were male and 37(41.11%) were females. Among 90 patients, 71(78.9%) patients were married. The mean BMI of the patients was 23.29±2.83 kg/m2. In our study 58(64.44%) patients were belonging to low SES, 26(28.89%) patients were belonging to middle and 6(6.67%) patients were belonging to high SES. The mean Hb level of the patients was 11.38±2.31 g/dl. In this study 0 grade of anemia was noted in 38(42.2%) patients, grade 1 was noted in 27(30.0%) patients, grade 2 was noted in 15(16.7%) patients and grade 3 was noted in 10(11.1%) patients. At baseline the mean absolute neutrophils count of the patients was 6.01±1.73 while at 48th hours the mean absolute neutrophils count of the patients was 4.63±5.12. Table 1
Out of 90 patients, neutropenia was noted in 45(50%) patients. Fig 1

In this study 0 grade of neutropenia was noted in 45(50%) patients, grade 1 was noted in 22(24.44%) patients, grade 2 was noted in 16(17.78%) patients, grade 3 was noted in 6(6.67%) patients and grade 5 was noted in 1(1.11%) patients. Fig 2

Table 1: Baseline features of patients

n	90
Age (years)	43.43 ± 11.73
Gender	
Male	53 (58.9%)
Female	37 (41.1)
Marital Status	
Married	71 (78.9%)
Unmarried	19 (21.1%)
BMI (kg/m2)	23.29 ± 2.83
Socioeconomic status	
Low	58 (64.4%)
Middle	26 (28.9%)
High	6 (6.7%)
Hemoglobin level (g/dl)	11.38 ± 2.31
Grades of anemia	
No anemia	38 (422%)
Mild	27 (30.0%)
Moderate	15 (16.7%)
Severe	10 (11.1%)
Absolute neutrophils count at presentation	6.01 ± 1.73
Absolute neutrophils count after 48 hours	4.63 ± 5.12

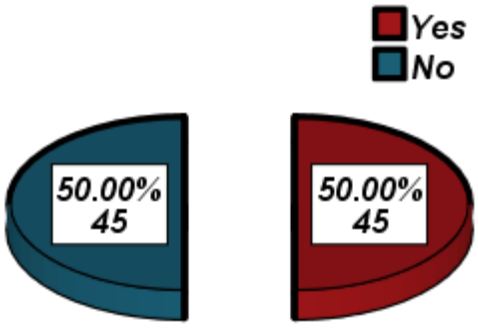

Fig 1: Frequency distribution of neutropenia

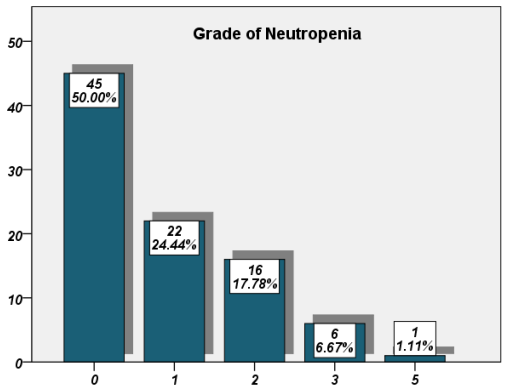

Fig 2: Frequency distribution of grades of neutropenia

DISCUSSION:

Chemotherapy is a viable treatment choice for lymphomas because of its curative potential. Chemotherapy, on the other hand, has limits of its own. Chemotherapy-induced neutropenia and infection are serious side effects that must be avoided at all costs. This neutropenia and the related fever/infection expenses are large and will certainly be a significant cost driver, particularly in developing nations.16, 17

Drug-induced neutropenia affects one person in a million per year, according to the CDC. Although the precise incidence of agranulocytosis is unclear, it is believed that between 1.0 and 3.4 cases per million people are diagnosed each year.18 Over 370,000 patients in Denmark were included in a research that discovered neutropenia in about 1 percent of regular full blood counts (CBCs). HIV infection, acute leukemias, and myelodysplastic syndromes were all linked to neutropenia.18

Neutropenia affects women more than men. It's possible that women are more likely than males to develop agranulocytosis due of their higher incidence of drug consumption. It's unclear if the greater frequency is linked to a rise in the number of female patients with autoimmune diseases. 19 In our study the mean age of the patients was 43.43±11.73 years. In this study Out of 90 patients 53(58.89%) were male and 37(41.11%) were females. Similar to our study results a study by Mohammad Nadeem et al17 showed that out of thirty patients, 73.3% were men while 26.6% were women. The mean age of patients in that study was 38±15.0 years. One study by Yong Won Choi et al14 showed in their study 57 years the mean age of the patients.

In our study out of 90 patients diagnosed with B-cell NHL on R-CHOP chemotherapy regimen, neutropenia was noted in 45(50%) patients. In a study done in Thailand20, 145 patients were investigated to suggest a prediction model for life-threatening neutropenia and febrile neutropenia following the first round of CHOP treatment with severe NHL. According to their findings, 39% of patients experienced life-threatening neutropenia during the first cycle of CHOP, and 33% developed febrile neutropenia. Rabinowitz et al. from the Lehey clinic conducted two more trials indicating the occurrence of neutropenia following cycle one CHOP treatment in lymphoma. Cycle one neutropenia has been shown in one research to be a warning indication of an elevated risk of mortality. Cycle 1 severe neutropenia affected 29.4% of the participants in the research.21 In another study, the same researchers proposed a model to predict neutropenia after cycle 1 CHOP.22 About 53% of patients (47–89) experienced severe neutropenia, with 70% of cases occurring during cycle 1. Most patients with severe neutropenia in the first cycle were over 65 years old, with 82 percent of these cases.

NHL affected around 4.3 million individuals in 2015, and 231,400 people died as a result. About 2.1% of persons in the United States will be afflicted at some time in their lives by this disease. The average patient is 65 to 75 years old when they are first diagnosed. Seventy-one percent of Americans survive five years.23-25 NHL is Australia's sixth most prevalent cancer, afflicting approximately 6,000 individuals each year.26 NHL is the 5th most frequent cancer in Canadian men and the 6th most common cancer in Canadian women. Males have a one in 44 lifetime chance of having lymphoid cancer, while females have a one in 51 chance.27, 28 An estimated 13,900 persons are diagnosed with NHL each year, on average, according to data collected between 2014 and 2016. It's the tenth most prevalent cause of cancer death in the UK, with about 4,900 fatalities each year.28 Statistics from 2012 to 2016 reveal that for every 100,000 adults, around 19.6 instances of NHL occur, and that for every 100,000 adults, about 5.6 individuals die from NHL each year. There are approximately 694,704 persons in the United States who have NHL. An estimated 2.2 percent of men and women will be diagnosed with NHL at some point in their lives.29

In a recent study, Yokoyama M et al reported that the incidence of neutropenia after the first cycle was observed in 9.1% (n=42) of B-NHL patients who were on R-CHOP regimen. All of the patients were fall in Grade-IV (very severe) neutropenia with ANC <0.5 x 109/L. They further evaluated that neutropenia was more prevalent in the patients with age >65 years (73.8%), female gender (59.5%), hemoglobin level <12g/dL (52.4%) and serum albumin >35 g/L (61.9%), ($P<0.05$).15

It was shown that individuals with NHL who received treatment frequently developed neutropenia. According to their findings, 30.8% of NHL patients experienced neutropenia of any grade after the first cycle of treatment, which included CHOP and R-CHOP. 30 Picozzi et al. found that after having CHOP chemotherapy, 24% of patients required hospitalisation due to febrile neutropenia.31 Cyclophosphamide, doxorubicin, vincristine, and prednisolone were the chemotherapeutic drugs used in a research conducted by Mohammad Nadeem et al., to determine the prevalence and severity of neutropenia in diffuse large B-cell lymphoma. 17

A research found that rituximab-containing intense chemotherapy often resulted in late onset neutropenia (LON), which they called a "common side effect." On average, patients had a follow-up of 411 days, and 23 of the 107 who acquired LON did so 106 days after their last round of treatment. There was a cumulative incidence of 24.9% of LON in all patients. The nadir neutrophil count was 0.61x109/l, which was the most common value.32

CONCLUSION:

This study concluded that approximately half of the total patients developed neutropenia who were diagnosed with B-cell NHL on R-CHOP chemotherapy regimen.

REFERENCES:

1. Devi AA, Sharma TD, Singh YI, Sonia H. Clinicopathological profile of patients with non-hodgkin's lymphoma at a regional cancer center in Northeast India. Journal of the Scientific Society 2017;44(3):140.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians 2015;65(2):87-108.
3. Bukhari U, Jamal S, Lateef F. NON HODGKIN'S LYMPHOMA" A STUDY. Pakistan Oral and Dental Journal 2015;35(3).
4. Tariq A, Aziz MT, Mehmood Y, Asghar SA, Khurshid A. Clinical Response to CHOP vs. R-CHOP in Adult Patients with Diffuse Large B-Cell Lymphomas. Asian Pacific journal of cancer prevention: APJCP 2018;19(5):1181.
5. Tariq A, Khurshid A, Mehmood Y. Potential Risk Factors and Prevalence Trend of Diffuse Large Beta Cell Lymphoma in Pakistani population. International Journal of Pharmaceutical Research & Allied Sciences 2015;4(3).
6. Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. Pathology 2018;50(1):74-87.
7. Martelli M, Ferreri AJ, Agostinelli C, Di Rocco A, Pfreundschuh M, Pileri SA. Diffuse large B-cell lymphoma. Critical reviews in oncology/hematology 2013;87(2):146-71.
8. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology 2015;26(suppl_5):v116-v25.
9. Qubtia M, Munawar K, Hamid MA, Badar F, Siddiqui N, Kazmi SA, et al. CHARACTERISTICS AND OUTCOME OF PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA-TREATED WITH CHEMOTHERAPY OR CHEMO-IMMUNOTHERAPY. Journal of Ayub Medical College Abbottabad 2016;28(2):254-8.
10. Salles G, Barrett M, Foà R, Maurer J, O'Brien S, Valente N, et al. Rituximab in B-cell hematologic malignancies: a review of 20 years of clinical experience. Advances in therapy 2017;34(10):2232-73.
11. Rojnuckarin P. High Incidence of Febrile Neutropenia in Non-Hodgkin Lymphoma Patients Receiving CHOP Chemotherapy despite G-CSF Prophylaxis. Journal of Hematology and Transfusion Medicine 2017;27(1):45-56.
12. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: an overview about well-established and recently emerging clinical data. Critical reviews in oncology/hematology 2017;120:163-79.

13. Dinan MA, Hirsch BR, Lyman GH. Management of chemotherapy-induced neutropenia: measuring quality, cost, and value. Journal of the National Comprehensive Cancer Network 2015;13(1):e1-e7.
14. Choi YW, Jeong SH, Ahn MS, Lee HW, Kang SY, Choi J-H, et al. Patterns of neutropenia and risk factors for febrile neutropenia of diffuse large B-cell lymphoma patients treated with rituximab-CHOP. Journal of Korean Medical Science 2014;29(11):1493-500.
15. Yokoyama M, Kusano Y, Takahashi A, Inoue N, Ueda K, Nishimura N, et al. Incidence and risk factors of febrile neutropenia in patients with non-Hodgkin B-cell lymphoma receiving R-CHOP in a single center in Japan. Supportive Care in Cancer 2017;25(11):3313-20.
16. Herold M, Hieke K. Costs of toxicity during chemotherapy with CHOP, COP/CVP, and fludarabine. The European Journal of Health Economics 2002;3(3):166-72.
17. Nadeem M, Idrees M, Khattak J, Hussain I, Amin Z, Arif S, et al. frequency and severity of neutropenia in diffuse large B-cell non hodgkin's lymphoma after first cycle of Chemotherapy comprising cyclophosphamide, Doxorubicin, vincristine with prednisolon. Journal of Ayub Medical College Abbottabad 2011;23(1):80-3.
18. Andersen C, Tesfa D, Siersma VD, Sandholdt H, Hasselbalch H, Bjerrum O, et al. Prevalence and clinical significance of neutropenia discovered in routine complete blood cell counts: a longitudinal study. Journal of internal medicine 2016;279(6):566-75.
19. Christopher D Braden. Neutropenia. 2018 [cited 2020]; Available from: https://emedicine.medscape.com/article/204821-overview.
20. Intragumtornchai T, Sutheesophon J, Sutcharitchan P, Swasdikul D. A predictive model for life-threatening neutropenia and febrile neutropenia after the first course of CHOP chemotherapy in patients with aggressive non-Hodgkin's lymphoma. Leukemia & lymphoma 2000;37(3-4):351-60.
21. Rabinowitz A, Weiner N, Steinberg D, Sparks J, Fridman M, Liberman R, et al. Severe neutropenia in cycle one of CHOP is a marker of early death among intermediate and high grade lymphoma (IHL) patients. Journal of Clinical Oncology 2004;22(14_suppl):6717-.
22. Rabinowitz AP, Weiner NJ, Tronic BS, Fridman M, Liberman RF, Delgado DJ. Severe neutropenia in CHOP occurs most frequently in cycle 1: a predictive model. Leukemia & lymphoma 2006;47(5):853-8.
23. Wang H, Naghavi M, Allen C, Barber R, Bhutta Z, Carter A, et al. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1459-544.
24. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The lancet 2016;388(10053):1459-544.
25. seer.cancer. Cancer Stat Facts: Non-Hodgkin Lymphoma. 2020; Available from: https://seer.cancer.gov/statfacts/html/nhl.html.
26. lymphoma, Auperin A, Michon J, Behrendt H, Leverger G, Frappaz D, et al. Non-Hodgkin Lymphoma Overview. 2020 [cited 2020]; Available from: https://www.lymphoma.org.au/page/9/non-hodgkin-lymphoma.
27. Ellison LF, De P, Mery LS, Grundy PE. Canadian cancer statistics at a glance: cancer in children. Cmaj 2009;180(4):422-4.
28. cancerresearchuk. Non-Hodgkin lymphoma statistics. 2020 [cited 2020]; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma.
29. seer.cancer. Cancer Stat Facts: Non-Hodgkin Lymphoma. 2020 [cited 2020]; Available from: https://seer.cancer.gov/statfacts/html/nhl.html.
30. M.H. Mengal, Z. Mehmood, C. Kapoor, M. Iqbal. Frequency of chemotherapy induced neutropenia in patients of non Hodgkin's lymphoma. 2014.

31. Morrison VA, Picozzi V, Scott S, Pohlman B, Dickman E, Lee M, et al. The impact of age on delivered dose intensity and hospitalizations for febrile neutropenia in patients with intermediate-grade non-Hodgkin's lymphoma receiving initial CHOP chemotherapy: a risk factor analysis. Clinical lymphoma 2001;2(1):47-56.
32. Nitta E, Izutsu K, Sato T, Ota Y, Takeuchi K, Kamijo A, 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):364-9.