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Refractory/Relapsed High-Grade B-Cell Lymphoma in the Elderly: A Special Therapeutic Challenge

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Abstract

BACKGROUND: According to the 2016 World Health Organization classification of lymphoid neoplasms, high-grade B-cell lymphoma (HGBL) is defined as a new category for aggressive diffuse large B-cell lymphomas (DLBCL), including DLBCL NOS as well.

CASE REPORT: An 80-year-old patient was admitted because of an enlargement of the lymph node located in the right neck region. The patient underwent 6 cycles of R-CHOP, which is considered to be the standard treatment for non-Hodgkin lymphomas (NHL) DLBCL (NOS) CSII B "Bulky," and he subsequently achieved complete remission (CR). A lymph node biopsy was performed, PH No. 12742/21, which revealed the following: LCA+, CD79 α CD20+, and CD5+, in approximately 50% of the cells, NHL DLBCL (NOS) was of GCB origin, etc. The international prognostic index risk score was 2, the cumulative illness rating scale score was 4. In addition, no bone marrow infiltration was reported. A COP-based chemotherapy protocol was administered, after which the evaluation showed disease relapse. Multi-slice spiral computed tomography (MSCT) follow-up showed an enlarged conglomerate of lymph nodes in all the neck levels. Dg: NHL DLBCL (NOS) CS IVB "Bulky" E (the hypopharynx). The echocardiography results were the following: (EF 50%, aortic insufficiency with MR1+, TR1+ of the aortic valve 3+). The patient was presented to the Consilium, who decided to apply the following therapy (Polatuzumab vedotin + Rituximab + Bendamustine). After III cycle of treatment, MSCT follow-up was performed. The patient gained weight, oral food intake was enabled, whereas the quality of life was significantly improved.

CONCLUSION: The administration of targeted therapies offers hope that more efficient treatment may be provided to elderly patients with relapsed HGBL.

Introduction

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of malignant lymphoid tumors, arising from B cells or T cells, that is, natural killer (NK) cells, remaining at various stages of differentiation [1]. The majority (85%) of NHLs are of B-lymphocyte origin, whereas the remaining 15% of NHLs are of T-cell or NK-cell origin and a mix of B-cell and T-cell origin. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, comprising a large number of different entities. Due to the presence of new diverse genetic, clinical, and immunophenotypic features found between lymphoid neoplasms, the new World Health Organization classification of lymphoid neoplasms was introduced in 2016 [1]. While summarizing the basic concept used in the classification of aggressive B-cell lymphomas along with the new findings, high-grade B-cell lymphoma (HGBL) was defined as a new separate entity, replacing the group of unclassifiable NHL DLBCL, which was later named "a gray zone lymphoma," as a category with features intermediate between DLBCL and the "Burkitt" lymphoma (BL). HGBL is subgrouped as HGBL with c-MYC translocation and Bcl-2 and/or Bcl-6 rearrangements, so-called double- or triple-hit lymphoma (HGBL-DH or HGBL-TH, respectively) and as NHL DLBCL NOS, the blastoid morphology of which lacks MYC and Bcl-2 and/or Bcl-6 rearrangements [2]. A common immunohistochemistry panel shows that HGBL is strongly positive for: CD20, BCL6, CD10, MYC, BCL2, Ki67, IRF4/MUM1, Cyclin D1, CD5, and CD23 [3].

During a complete patient examination, it is necessary to establish the level of disease progression, that is, its clinical stage. As regards the four stages of clinical disease, the Ann Arbor staging classification for Hodgkin's disease was initially adopted in 1971, but it is currently applied not only for NHL DLBCL, but for HGBL as well. A special emphasis is placed on extranodal localization with an addition of the capital letter E. Special consideration is given to cases of bulky disease, simultaneously pointing at the large tumor mass [4]. A prognostic risk category of each patient is calculated using the international prognostic index (IPI). The IPI score is established for patients over 60 years of age, whereas the age-adjusted IPI is established for those younger than 60 years. IPI is a useful clinical method for classifying patients into differentiated risk groups.

However, it does not take into consideration a genetic spectrum. HGBL is commonly characterized by poor prognostic parameters, such as the following: Elevated serum LDH, bone marrow (BM) and CNS involvement, and high IPI score, especially in relapse [5].

Elderly patients are found to be most commonly affected by a number of comorbidities (such as cardiovascular diseases, hypertension, diabetes, and renal insufficiency), which severely limit the overall therapeutic efficiency. Therefore, the cumulative illness rating scale (CIRS), an organ-system-based rating scale used for the purpose of disease assessment can be useful when making treatment decisions. Higher IPI scores are associated with poorer prognosis and they reduce the possibility of applying a more aggressive therapy in "unfit" elderly DLBCL patients, not only when it comes to the first line of treatment, but they even further limit the possibility of treatment of the relapsed or refractory disease as well. The IPI score refers to the patients aged over 65. However, it seems not to be enough for the assessment of those patients who are in the eighth or even ninth decade of life.

Case Report

An 80-year-old patient was admitted to hospital because of an enlargement of the lymph node in the right neck region. The enlarged lymph node was not painful, with no skin changes reported in the adjacent area. He had allegedly lost 10 kg for the past 2 months, whereas no fever or night sweats were reported.

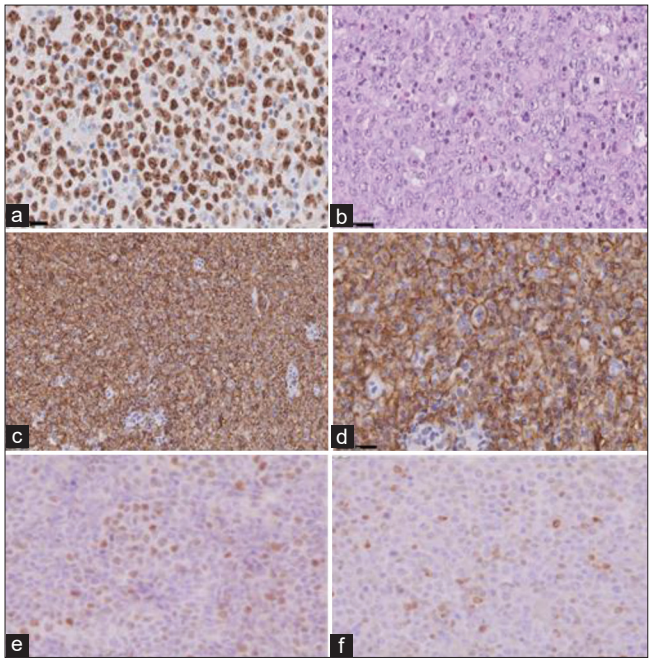

Figure 1: A lymph node biopsy (a.H&E ×40) and immunohistochemistry (b. Ki 67 × 40, c. CD20 × 40, d.CD20 × 20, e. Bcl2 × 40, f.Bcl6 × 40)

The patient anamnesis revealed that the patient had previously undergone 6 cycles of R-CHOP as the standard treatment for NHL DLBCL (NOS) CSII B "Bulky" and that he subsequently achieved complete remission (CR), the state of which he was able to maintain over the following 34-month period. He was a patient diagnosed with cardiac ischemic disease and diabetes mellitus, for which he received oral antidiabetic drugs. In addition, he had elevated blood pressure, stenosis valvulae aortae, heart rhythm disorder, and showed no signs of drug hypersensitivity.

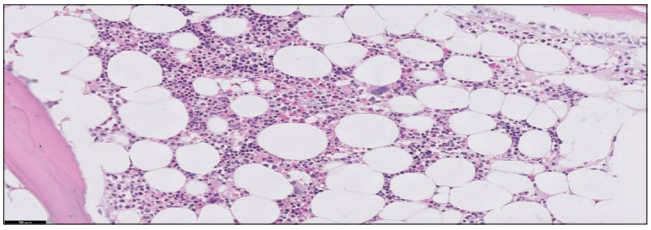

Figure 2: Bone marrow (BM) trephine biopsy, showing normal BM (H&E 20×)

A lymph node biopsy was performed in the right neck region, and the obtained pathohistological finding or PH No. 12742/21 revealed the following: LCA+, CD79 α, CD20+, CD5+, BCL2+, and BCL6+, Ki 67 + in approximately 50% of the cells, NHL DLBCL (NOS) was of GCB origin, (Figure 1).

To adequately assess the clinical stage of the patient ("staging"), blind BM biopsy was performed, PH No. 13741/21: The results of which indicated a lack of infiltration by the lymphoproliferative disease (LPD) (Figure 2).

The blood test results showed the following (Table 1), whereas normal reference intervals were established for other biochemical parameters except for C-reactive protein (CRP) and LDH. Hemostasis testing showed values within the normal reference range.

Table 1: Laboratory results (all within reference range, except for LDH and CRP)

WBC	9.0 × 10*9
Neutrophils	11.4 × 10*9
Lymphocytes	1.3 × 10*9
Monocytes	0.6 × 10*9
Eosinophils	0.6 × 10*9
Basophils	0.04 × 10*9
Rbc	3.46 × 10*12
Hgb	120 g/L
MCV	89 fl
MCH	29.3 pg
MCHC	333 g/l
Plt	286x10*9
LDH	1976 U/L
CRP	36.5 mg/L
AST	40 IU/l
ALT	22 IU/L
GGT	49 IU/L
ALP	91 U/L
Bilirubin total	18 umol/L
Bilirubin direct	3.4 umol/L
urea	9.4 mmol/L
creatinine	79 umol/L
K	4.5 mmol/L
Na	137 mmol/L
Ca	2.54 mmol/L
glucose	6.9 mmol/L
Fe	12.8 umol/L
Ferritin	330 ug/L
TIBC	54 umol/L
UIBC	41 umol/L

CRP: C-reactive protein, WBC: White blood cells, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration.

The following diagnosis was established: NHL DLBCL (NOS) CS IIB relapse. The calculated IPI risk score was 2 (low-intermediate risk), the CIRS score was 4. A COP-based chemotherapy protocol was administered (Endoxan + Oncovin + Prednison), after which the evaluation showed disease progression.

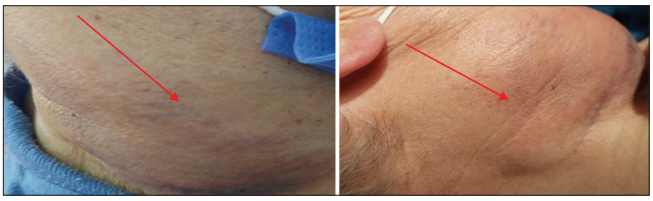

Figure 3: The physical examination (inspection and palpation) (hard conglomerate of lymph nodes measuring 8 cm × 6 cm on the right side of neck region) – the disease progression

Multi-slice spiral computed tomography (MSCT) follow-up showed an enlarged conglomerate of lymph nodes (10 cm × 4 cm × 5 cm) in all the neck levels, infiltrating the hypopharinx as well. Dg: NHL DLBCL (NOS) CS IVB "Bulky" E (the hypopharynx). BM biopsy was performed again, but there was no lymphoproliferative infiltration. The patient refused a lumbal puncture. However, he had no CNS symptoms. The calculated IPI risk score was 3 (high-intermediate risk), the CIRS score was 4. The results of a physical examination revealed that the tumor mass led to an inability to swallow, extending to the uvula on the left, with peripheral lymphadenopathy of the right cervical and supraclavicular lymph nodes (Figures 3-5).

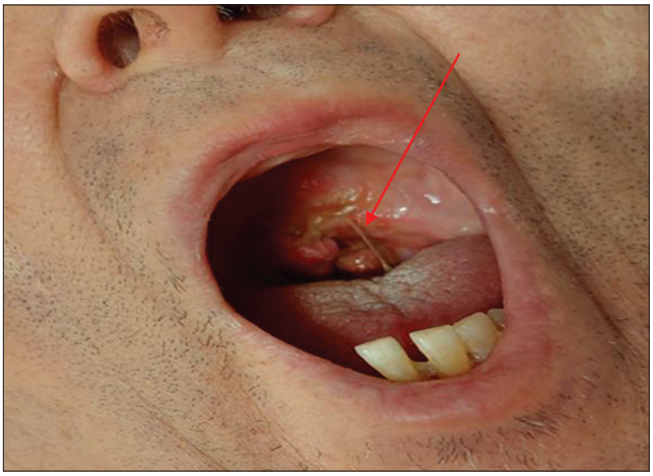

Figure 4: The physical examination (inspection) (tumefact of the left palatal arch with dislocation of the uvula) – the disease progression

Follow-up was performed along with the echocardiography (EF 50%, aortic insufficiency with MR1+, TR1+ of the aortic valve 3+). Specific problems occurred, resulting from the fact that the patient was old, had a number of comorbidities, and was not suitable for the administration of aggressive chemotherapy. The decision for the administration of the appropriate therapy (Polatuzumab vedotin + Rituximab + Bendamustine) was made, bearing in mind that it was the only possible option available. After receiving III cycle of treatment, MSCT follow-up was performed (revealing an enlarged right lymph gland, the current proportion of which was 3 cm × 2 cm), while the rest of the finding results

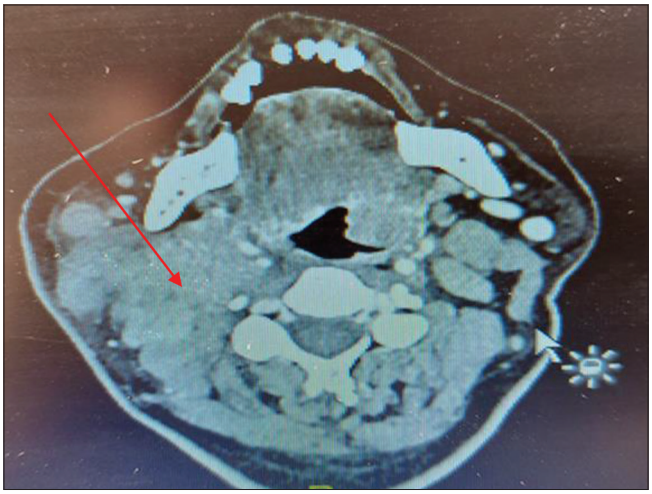

Figure 5: The disease progression – evaluated using MSCT (a tumor in the left tonsillar area filled and infiltrated into a large section of the oropharynx with the alteration 10 cm × 4 cm × 5 cm in diameter, compressing and narrowing the air pillar. The review of all floors of the neck demonstrated bilaterally pathological thyroid glands from 35 mm × 48 mm in diameter to the conglomerate on the right 85 mm × 65 mm in diameter)

revealed CR (Figures 6 and 7). The patient was gaining weight; oral food intake was enabled, whereas the quality of life was significantly improved.

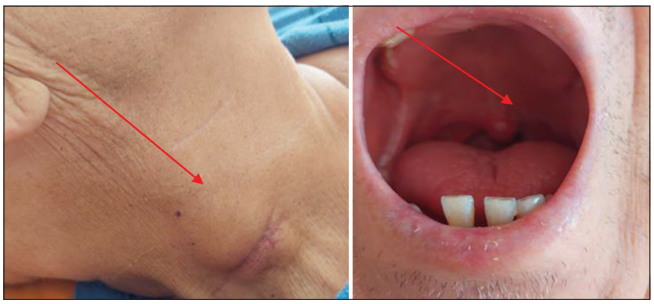

Figure 6: The response achieved after 3 cycles of treatment (using the inspection method) – regression of the tumor mass (lagging lymph gland on the right neck diameter 3 cm × 2 cm and tumefact of the left palatal arch has disappeared)

Discussion

Although the incidence of HGBL, NOS is low, accounting for 3% of the adult invasive B-cell lymphomas, and has a median age of onset of 55 (18–80) years, incidences are higher in males than in females. Patients with HGBL and NOS often present with an elevated LDH, BM and CNS involvement, and a high IPI score [6].

The patient, who was 76 at the time of his first diagnosis, presented with elevated LDH values and IPI score (low-intermediate risk), but with no BM or CNS infiltration being reported. CT CNS was normal.

In the context of relapsed disease occurring 3 years and 4 months later, the presentation of the

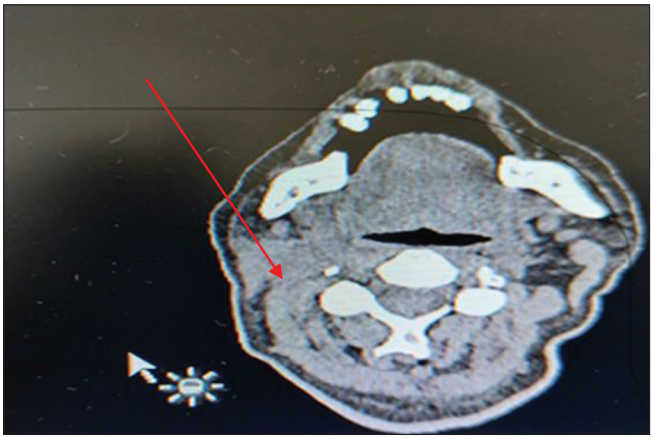

Figure 7: The response achieved after 3 cycles of treatment (Polatuzumab vedotin + Bendamustine + Rituximab) – Multi-slice spiral computed tomography (As regards the hypopharynx, larynx, and tonsillar area, no morphological and structural changes, which were previously depicted on the left of the neck region, were observed; whereas the lymph gland 25 mm × 23 mm × 30 mm in diameter was located on the right of the neck region)

previously described poor prognostic parameters showed elevated LDH values, male gender, and a low-intermediate IPI score. The complete blood count along with all the relevant biochemical analyses showed that the parameters were within the reference range, except for the elevated CRP and LDH levels with no infection being detected (the urine culture test, chemoculture, and nasopharyngeal swab were sterile).

Previously mentioned diagnostics, complete with the assessment of disease extent and prognostic assessment of patients and their clinical profiling, undoubtedly raise the question of how to treat patients diagnosed with HGBL, not only when it comes to their initial treatment, but when they are in relapse or in case of the progression of the disease, which makes this question even harder to respond. Numerous retrospective observational studies have shown that standard treatment performed according to the R-CHOP (Rituximab + Endoxan + Adriablastin + Oncovin + Prednison) regimen in patients who are carriers of gene mutations (such as c-Myc, Bcl-2 and/or Bcl-6), results in significantly poorer survival rates when compared to patients with NHL DLBCL who are not carriers of such aberrations. Thereby, the study conducted by Rosenwald *et al*., which analyzed a cohort of 2383 respondents who received R-CHOP chemotherapy – demonstrated that PFS and OS were shorter in patients who were carriers of the c-Myc rearrangement associated with Bcl-2 and/or Bcl-6 [7]. Dunleavy *et al*. conducted a prospective multicentric study that comprised 53 patients with aggressive B-cell lymphomas, 44% of which had the c-Myc rearrangement (SH), whereas 56% of patients (with DHL/THL) who were treated with DA-EPOCH-R, reported no statistically significant difference in EFS and OS (71% vs. 77%) between SH and DHL/THL during the 4-year observation period. However, the fact that it was a small sample size must be taken into account [8]. The French retrospective study carried out by Laude *et al*., which comprised 160 patients with HGBL (81% DHL and 19% THL) showed a significantly higher PFS compared to those who received intensive chemotherapy as opposed to R-CHOP [9]. The standard therapeutic regimen has not been established. In accordance with this fact and general condition of the patient presented above, he was treated by the available COP (Endoxan + Oncovin + Prednisolon) protocol. Considering the fact that retrospective studies reveal no data of intensive chemotherapy as being superior, these patients should be involved in clinical trials, the subject of which is the examination of targeted therapies supporting the key mechanism of pathogenesis of Myc and Bcl-2 activation.

On one hand, until then, intensive chemotherapy was administered in patients who were able to receive such a therapy, particularly the ones with a high IPI score (a personalized approach from DA-EPOCH-R to R-Hyper-CVAD and R-IVAC), but on the other hand, with regards to the patients who were not considered as eligible candidates for high-dose (HD) chemotherapy or TMHC due to the presence of comorbidities or advanced age – we returned to the treatment with R-CHOP, R-COEP), and then to the treatment of patients with relapsed/refractory DLBCL (R CEPP, Polatuzumab vedotin + Rituxam + Bendamustine), radiation therapy as a local treatment modality, the involvement of patients in the clinical trials, eventually turning to the best supportive care as the worst possible option.

The patient presented above showed the progression of the disease despite receiving the therapy, at the point when HGBL/NOS came under the spotlight, with an elevated LDH, extranodal localization, and an IPI score changing to a high-intermediate risk [6].

HGBL at diagnosis remains a major therapeutic challenge. The question of how to choose the most effective therapeutic strategy is still an open one. Of key importance is the further investigation of underlying pathophysiological mechanisms of this particular group of LPD, along with an understanding of interactions between genetic alterations and lymphomagenesis [10].

Numerous promising research studies are currently being conducted, primarily the ones targeting at c-MYC and Bcl-2. A series of recent studies has indicated the importance of implementing new treatment strategies, such as the application of newly approved anti-CD19 monoclonal antibodies and chimeric antigen receptor T-cells in the treatment of patients diagnosed with high-risk NHL DLBCL and HGBL, who do not achieve a complete clinical response to the previously applied therapy. Elderly patients with or without comorbidities represent a specific problem, which means that they have limited treatment options. DLBCL is the most common lymphoma subtype among adults in the Western World. With a median age at diagnosis of 70 years and increasing incidence with advanced age,

the number of newly diagnosed elderly patients with DLBCL becomes larger every year as life expectancy increases. Patients with transplantation – ineligible relapsed/refractory (R/R) diffuse large B cell lymphoma (DBCL) fare poorly, with limited treatment options. The antibody-drug conjugates polatuzumab vedotin targets CD79 b, a B cell receptor component. Polatuzumab vedotin combined with BR (Bendamustine + Rituximab) resulted in a significantly higher CR rate and reduced the risk of death by 58% compared with BR (bendamustine + rituximab) in patients with transplantation – ineligible R/R DBCL [11]. Age itself does not constitute a contraindication to standard treatment of DLBCL, but its association with frailty and the presence of comorbidity means that individual assessment is necessary to determine treatment feasibility and safety [12].

Conclusion

The administration of targeted therapy offers hope that more efficient treatment may be provided to elderly patients diagnosed with HGBL, particularly to the ones being in relapse, and those who are not found to be suitable for the HD chemotherapy and transplantation. Perhaps, we made a mistake at the point when chemoimmunotherapy (Polatuzumab vedotin + Rituxam + Bendamustine) was not given immediately after the diagnosis of relapse was established.

References

1. Wu SC, Tsang P. Lymphoma and related disorders, General WHO classification-B cell, PubMed Search: WHO classification of B cell lymphoid neoplasms 2016.
2. Olszewski AJ, Kurt H, Evens AM. Defining and treating high-grade B-cell lymphoma, NOS, Blood. 2022;140(9):943-54. https://doi.org/10.1182/blood.2020008374
   PMid:34525177
3. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90. https://doi.org/10.1182/blood-2016-01-643569
   PMid:26980727
4. Jaffe ES. The 2008 WHO classification of lymphomas: Implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program. 2009;(8):523-31. https://doi.org/10.1182/asheducation-2009.1.523
   PMid:20008237
5. McMillan AK, Phillips EH, Kirkwood AA, Barrans S, Burton C, Rule S, *et al.* Favourable outcomes for high-risk diffuse large B-cell lymphoma (IPI 3-5) treated with front-line R-CODOX-M/R-IVAC chemotherapy: Results of a phase 2 UK NCRI trial. Ann Oncol. 2020;31(9):1251-9. https://doi.org/10.1016/j.annonc.2020.05.016
   PMid:32464282
6. Li S, Lin P, Medeiros LJ. Advances in pathological understanding of high-grade B cell lymphomas. Expert Rev Hematol. 2018;11(8):637-48. http://doi.org/10.1080/17474086.2018.1494567
   PMid:29989509
7. Rosenwald A, Bens S, Advani R, Barrans S, Copie-Bergman C, Elsensohn MH, *et al.* Prognostic significance of MYC rearrangement and translocation partner in diffuse large B-cell lymphoma: A study by the Lunenburg lymphoma biomarker consortium. J Clin Oncol. 2019;37(35):3359-68. https://doi.org/10.1200/JCO.19.00743
   PMid:31498031
8. Dunleavy K, Fanale MA, Abramson JS, Noy A, Caimi PF, Pittaluga S, *et al.* Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: A prospective, multicentre, single-arm phase 2 study. Lancet Haematol. 2018;5(12):e609-17. https://doi.org/10.1016/S2352-3026(18)30177-7
   PMid:30501868
9. Laude MC, Lebras L, Sesques P, Ghesquieres H, Favre S, Bouabdallah K, *et al.* First-line treatment of double-hit and triple-hit lymphomas: Survival and tolerance data from a retrospective multicenter French study. Am J Hematol. 2021;96(3):302-11. http://doi.org/10.1002/ajh.26068
   PMid:33306213
10. Novo M, Castellino A, Nicolosi M, Santambrogio E, Vassallo F, Chiappella A, *et al*. High-grade B-cell lymphoma: How to diagnose and treat. Expert Rev Hematol. 2019;12(7):497-506. https://doi.org/10.1080/17474086.2019.1624157
    PMid:31150587
11. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, *et al*. Polatuzumab vedotin in relapsed or refractery diffuse large B-cell lymphoma. J Clin Oncol. 2020;38(2):155-65. https://doi.org/10.1200/JCO.1900172
    PMid:31693429
12. Wasterlid T, Murphy S, Villa D, El-Galaly TC. Diffuse large B-cell lymphoma among the elderly: A narrative review of current knowledge and future perspectives. Ann Lymphom. 2022;6:6. https://doi.org/10.21037/aol-22-2