

# Triple-hit lymphoma in a 95-year-old patient: a case report and literature review

**Dongsheng Tang**

the Huai'an Clinical College of Xuzhou Medical University

**Yue Chen**

the Huai'an Clinical College of Xuzhou Medical University

**Yuye Shi**

the Huai'an Clinical College of Xuzhou Medical University

**Hong Tao**

the Huai'an Clinical College of Xuzhou Medical University

**Shandong Tao**

the Huai'an Clinical College of Xuzhou Medical University

**Quan'e Zhang**

the Huai'an Clinical College of Xuzhou Medical University

**Banghe Ding**

the Huai'an Clinical College of Xuzhou Medical University

**Zhengmei He**

the Huai'an Clinical College of Xuzhou Medical University

**Liang Yu**

the Huai'an Clinical College of Xuzhou Medical University

**Chunling Wang** (✉ [wcl6506@163.com](mailto:wcl6506@163.com))

the Huai'an Clinical College of Xuzhou Medical University

---

## Case Report

**Keywords:** Very elderly, Diffuse large B-cell lymphoma, High grade B cell lymphoma, Triple-hit lymphoma, Chemotherapy, Precision medicine

**Posted Date:** March 17th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1455879/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Introduction:** Diffuse large B cell lymphoma (DLBCL) is a highly heterogeneous tumor mainly occurring in the elderly, with approximately 40% of cases occurring in patients over 70 years old and this proportion will increase in the future. High grade B cell lymphomas (HGBL) with MYC and BCL2 and BCL6 rearrangements, so called triple-hit lymphomas (HGBL-THL), which usually presents a high-aggressive clinical behavior as well as to be associated with a very poor outcome. However, there are no standard treatment strategies for very elderly HGBL-DHL/THL patients, it still remains a challenge for clinicians.

**Case Presentaion:** we report a case of a 95-year-old patient diagnosed with diffuse large B-cell lymphoma (HGBL-THL, non-germinal central type, stage IV group A, IPI 5 points, high risk group), coronary atherosclerotic heart disease (paroxysmal atrial fibrillation, cardiac insufficiency), hypertension, treated with chemotherapy, radiotherapy and targeted drug therapy obtained better outcome of keeping alive for 1 year.

**Conclusion:** For very elderly HGBL-THL patients, a careful assessment of performance, nutritional status and comorbidities are needed before treatment. Novel therapies including immunotherapy, targeted therapy and chimeric antigen receptor T (CAR-T) cell therapy may provide benefit.

## Introduction

DLBCL is the most common aggressive type of non-Hodgkin lymphoma (NHL), which mainly occurred in older patients. About 50% of patients are over 65 years old and 15% are over 80s[1]. DLBCL older than 80 years old are defined as very elderly patients with poor outcome. High-grade B-cell lymphoma (HGBL) involving MYC and BCL2 and/or BCL6 rearrangement, so called double-hit or triple-hit lymphoma (DHL or THL), is a newly type defined in the 2016 World Health Organization classification[2]. HGBL represents approximately 8%-10% of de novo DLBCL and with a higher incidence (20%) in transformed indolent B-cell lymphoma[3, 4]. Patients with DHL and THL are known to have a well-known dismal prognosis with traditional chemotherapy, such as R-CHOP (rituximab, cylophosphamide, doxorubicin, vincristine, and prednisone). The best treatment for DHL and THL, especially for very elderly patients, is still unclear. Here we report a case of a 95-year-old very elderly HGBL-THL patient treated with chemotherapy, radiotherapy and targeted drug therapy obtained better outcome of keeping alive for 1 year, and review relevant literature to discuss the treatment progress of very elderly HGBL-DHL/THL.

## Case Presentation

A 95-year-old man developed slowly growing painless lymphadenopathy on the right side of the neck in July 2018. In August 2018, he was admitted due to gradually aggravated chest tightness. Upon initial evaluation, he was found to have an approximately 6cm×4cm mass on the right neck, with tough texture, no tenderness, clear boundary with surroundings, and poor mobility. Laboratory tests were as follows: WBC  $4.51 \times 10^9$  cells/L, RBC  $4.12 \times 10^{12}$  cells/L, Hb 120g/L, PLT  $191 \times 10^9$  cells/L. The

Electrocardiograph (ECG) revealed atrial fibrillation, the Coronary Computed Tomography Angioplasty (CTA) revealed mild stenosis of left anterior descending branch; the Computed Tomography (CT) of abdomen and whole neck revealed retroperitoneal enlarged lymph nodes, with multiple enlarged lymph nodes on the right side of the neck. The biopsy of the neck mass showed that lymphoid tissue proliferation with obvious atypia. Subsequently, Immunohistochemistry revealed CK-pan-, CD20+, PAX-5+, CD3-, CD5-, CD43-, CD21-, CD23-, CD10+, BCL-6+, CD30-, BCL-2+, CyclinD1-, MUM-1-, CD38+, Igκ(+/-), Igλ(+/-), Ki-67(>90%+), EBER-, TdT-, CD34-, C-Myc (+/-). Pathological diagnosis of diffuse large B cell lymphoma (non-germinal central type). Fluorescence in situ hybridization (FISH) analysis revealed MYC, BCL-2 and BCL-6 gene rearrangement (see Figure 1). After the evaluation of positron emission tomography/computed tomography (PET/CT), lung, liver, stomach and bone marrow were involved (see Figure 2). This patient was diagnosed with diffuse large B-cell lymphoma (HGBL-THL, non-germinal central type, stage IV group A, IPI 5 points, high risk group). On August 30, 2018, he was given reduced dose of RVP (rituximab 500 mg, vindesine 4 mg, and hydrocortisone 60mg) regimen (body surface area is 1.994m<sup>2</sup>), and on September 27, reduced-dose RCOP (rituximab 700mg, cyclophosphamide 0.4g, vindesine 4mg, hydrocortisone 60mg) was given, the tumor was smaller and the systemic symptoms were improved under treatment. In October 2018, the patient's neck lymph nodes increased and compression symptoms were presented than before, the CT of the whole body showed a mass of the right supraclavicular fossa, size 10cm×15cm, multiple mediastinal lymphadenopathy. Reduced-dose RCNOP (rituximab 700mg, cyclophosphamide 0.4g, mitoxantrone 4mg, vindesine 4mg, prednisone 40mg) regimen was given on October 21, and the tumor was significantly reduced, but the remission duration was less than 1 month and tumor swelled again. On November 15 and December 12, RCOP plus ibrutinib (rituximab 700mg, cyclophosphamide 0.6g, vindesine 4mg, prednisone 60mg, ibrutinib 420mg) regimen was given two courses of treatment. On January 6, 2019, he received reduce dose RCNOP plus ibrutinib (rituximab 700mg, cyclophosphamide 0.6g, vindesine 4mg, mitoxantrone 2mg, prednisone 60mg, ibrutinib 420mg) regimen. Pulmonary infection occurred and the infection was controlled after anti-infection treatment, the tumor mass was significantly reduced. Therefore, the patient stopped chemotherapy for 3 months on his own and maintenance therapy with ibrutinib. In April 2019, right cervical lymph nodes enlarged again, and low-dose local radiotherapy was given for 1 week, the tumor mass shrank again, but recurrence of lung infection and atrial fibrillation, after anti-infection treatment, he was given R<sup>2</sup> (rituximab 700mgd0, lenalidomide 25mgd1-5) regimen combined with prednisone 60mgd1-5 on May 16. On June 10, he was admitted to the hospital for palpitations and asthma. The electrocardiogram revealed rapid ventricular rate atrial fibrillation, and the asthma was progressively exacerbated. He was treated with methylprednisolone plus low-dose cyclophosphamide. Unfortunately, the treatment was ineffective and the patient died at 16:00 on July 13, 2019. (the treatment procedure of this patient see Figure 3)

## Discussion

DLBCL is a complex and heterogeneous disease and age is an independent adverse prognostic factor. Very elderly patients older than 80 years have a worse prognosis. Grim prognosis in older patients are

likely various reasons, which is related to its molecular mechanism, comorbidities, reduced treatment intensity and treatment-related toxicity. It is currently recognized that unfavorable genetic characteristics such as ABC subtypes, increased BCL2 expression, and high genome complexity were significantly associated with patient's age[5].

In order to prolong the survival of elderly DLBCL patients, researchers have made many explorations for a good balance between effectiveness and tolerability. Research has demonstrated that reduced-dose regimens can provide a better balance of benefit and risk for very elderly patients. In a prospective study by Peyrade et al. used R-miniCHOP regimen, a subgroup of 149 patients older than 80 years was analyzed for efficacy and toxicity, the 2-year progression-free survival (PFS) was 47% and overall survival (OS) was 59%, and most side-effect was haematological toxicity (grade  $\geq 3$  neutropenia occurred in 59 patients, febrile neutropenia occurred in 11 patients)[6]. Similarly, Wen-Hao Zhang et al. reported that a retrospective study of 31 patients with a median age of 79 years, treated with reduced-dose REPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) regimen, the complete remission rate (CR) was 71.0%, 3-year OS and PFS were 62.8% and 60.3%, respectively, treatment-related toxicities were generally tolerated and acceptable[7]. Another way to improve the tolerance of chemotherapy is called "pre-phase treatment", which refers to the application of vincristine and prednisone for 7 days before first chemoimmunotherapy cycle. In the NHL-B2 study, the first chemotherapy cycle of treatment-related mortality was decreased from 5% to less than 2% after the introduction of pre-phase treatment[8]. Chelsea et al. explored incorporating consolidative radiation therapy (RT) to reduce overall chemotherapy drug exposure, they found age older than 80 years who with early-stage patients, 3 to 4 cycles of chemotherapy followed by RT of disease free survival (DFS), PFS, OS ( $P=0.78$ ,  $P=0.654$ ,  $P=0.852$ ) were equivalent to chemotherapy alone and was associated with less toxic reaction, which suggested that RT following short chemotherapy may be a better choice for some early-stage elderly patients who could not tolerate standard course of chemotherapy[9]. A study from the Swedish Lymphoma Register showed that very elderly patients seem to benefit from rituximab-anthracycline-based treatment[10]. However, most of very elderly patients are associated with an increasing risk of coronary artery diseases, the use of potentially cardiotoxic drugs such as anthracycline-based chemotherapy may not tolerate. Doxorubicin could be replaced with mitoxantrone, etoposide, liposomal doxorubicin, gemcitabine. In addition, in order to better tailor therapeutic schemes for very elderly patients, a careful assessment is necessary. Comprehensive Geriatric Assessment (CGA) is an effective strategy to identify elderly patients who can benefit from a curative approach by activity of daily living (ADL), instrumental activity of daily living (IADL), and comorbidities[11]. Merli et al. develop a simplified geriatric assessment (sGA) to assess physical condition and defines a new prognostic index (EPI)[12]. These evaluation methods have helped in the prediction of mortality and the choice of treatment.

In recent years, some of clinic trials incorporating novel targeted drug have been evaluated. Gini et al. reported that 24 patients with a media age of 83 who received R<sup>2</sup>regimen have shown preferential activity in patients with an ORR of 50%[13]. Ibrutinib, as the first novel and effective oral BTK inhibitor (BTK inhibitors, BTKi), has been approved by the FDA for the treatment of B-cell malignancies. A randomized

multicenter phase III trial comparing ibrutinib plus RCHOP with placebo plus RCHOP in 838 DLBCL patients. Ultimately, ibrutinib plus RCHOP improved event-free survival (EFS), PFS and OS with manageable safety in patients age younger than 60 years. Nonetheless, in patients older than 60 years, ibrutinib plus RCHOP worsened EFS, PFS and OS, increased serious adverse events[14]. It showed that ibrutinib plus standard RCHOP may not appropriate for elderly patients, but treatment value of ibrutinib combined with reduced-dose chemotherapy worth further studying. The SENIOR study evaluated Lenalidomide combination with R-miniCHOP chemotherapy. However, the addition of lenalidomide to R-miniCHOP did not improve OS while resulted in more adverse events[15]. Recently, Schmitz and colleagues develop a new classification of DLBCL: MCD, BN2, N1 and EZB[16]. The genetic subtypes of DLBCL differ significantly in response to standard immunochemotherapy, and may also differ in response to targeted therapies. It is expected heterogeneous groups classified by molecular genetic testing that can be targeted and may improve the curative effect.

Triple-hit lymphoma with MYC, BCL-2 and BCL-6 rearrangements has a dismal prognosis, which occurs mainly in the elderly, with advanced stage (III/IV), higher risk of extranodal disease including central nervous system (CNS) and bone marrow involvement, elevated levels of lactate dehydrogenase (LDH) and higher International Prognostic Index (IPI) score[17]. R-CHOP is largely unsatisfactory, and patients may benefit from intensive treatment and hematopoietic stem cell transplantation (HSCT). Unfortunately, the median OS of DHL/THL is only 5 to 18 months even after intensive chemotherapy and/or HSCT[18]. A largest series report in Europe about the treatment of DHL/THL showed PFS was obviously longer with intensive regimen (R-ACVBP, R-COPAIDE, DA-R-EPOCH) for advanced stage (III/IV) patients, whereas was not significantly associated with OS. In addition, there was no difference in PFS and OS between R-CHOP group and intensive chemotherapy group among older than 65 years patients[4]. CAR-T cell therapy may present another potentially therapeutic option for HGBL-DHL/THL patients. The ZUMA-1 trial evaluated axicabtagene ciloleucel, an autologous anti-CD19 CAR-T cell, with an objective response rate of 83%, CR of 58%, respectively, of the 7 patients were HGBL-DHL/THL, there was still a objective response of 90% and CR of 33% of them[19]. Additionally, the results of the ZUMA-1 study showed that CAR-T therapy was equally effective in elderly patients (age  $\geq$  65 years), with a ORR rate of 92%, a CR rate of 75%, and did not seem to be affected by age in efficacy and safety[20]. However, how to maintain long-term curative effect of CAR-T is still a problem that needs to be solved. Currently, the management of HGBL-DHL/THL still present a challenge and the best treatment regimen remains unknown. Therefore, novel and effective treatments should be given priority and clinical trials should be considered. The ongoing clinical trials are as follows: Polatuzumab Vedotin combination with R-CHP(NCT04479267). Venetoclax (ABT199) plus chemoimmunotherapy (R-CHOP, DA-EPOCH-R) (NCT03984448). DA-EPOCH-R induction followed by Nivolumab consolidation (NCT03620578). Acalabrutinib in combination with CAR-T(NCT04257578). Glofitamab or Mosunetuzumab in combination with gemcitabine and oxaliplatin (Glofit-GemOx or Mosun-GemOx) (NCT04313608).

## Conclusion

Here we report this very elderly triple-hit lymphoma patient who have adverse genetic characteristics and cardiac complications, will probably die in short term due to the increasing neck mass compressing the airway without additional treatment. But the patient obtained long-term survival of 1 year after comprehensive treatment. Given our clinical experience, positive treatment can prolong survival should be always considered rather than giving up easily. In addition, multimodal therapy including reduced dose chemotherapy, radiotherapy and targeted drug therapy are recommended for those patients. However, our limitation is that we do not apply molecular genetic testing for patients and fail to select targeted drugs more accurately. Currently, very elderly DHL/THL is still a challenge for clinicians. Immunotherapy, targeted therapy, CAR-T therapy and other novel approach may have the potential to improve the outcome of very elderly HGBL-DHL/THL patients.

## **Declarations**

### **Acknowledgements**

Not applicable.

### **Funding**

Funded by Jiangsu Commission of Health (H2019082).

### **Availability of data and materials**

Not applicable.

### **Authors' Contributions**

Liang Yu and Chunling Wang contributed to thesis selection and design, Dongsheng Tang and Yue Chen gathered all patient data and prepared the original version of the manuscript, Yuye Shi and Hong Tao prepared the images. Shandong Tao, Quan'e Zhang, Banghe Ding and Zhengmei He were involved in data analysis. All authors read and approved the final manuscript.

### **Ethics approval and consent to participate**

The case report was approved and supervised by the ethics committee of the Huai'an Clinical College of Xuzhou Medical University.

### **Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editors-in-Chief of this journal.

### **Competing interests**

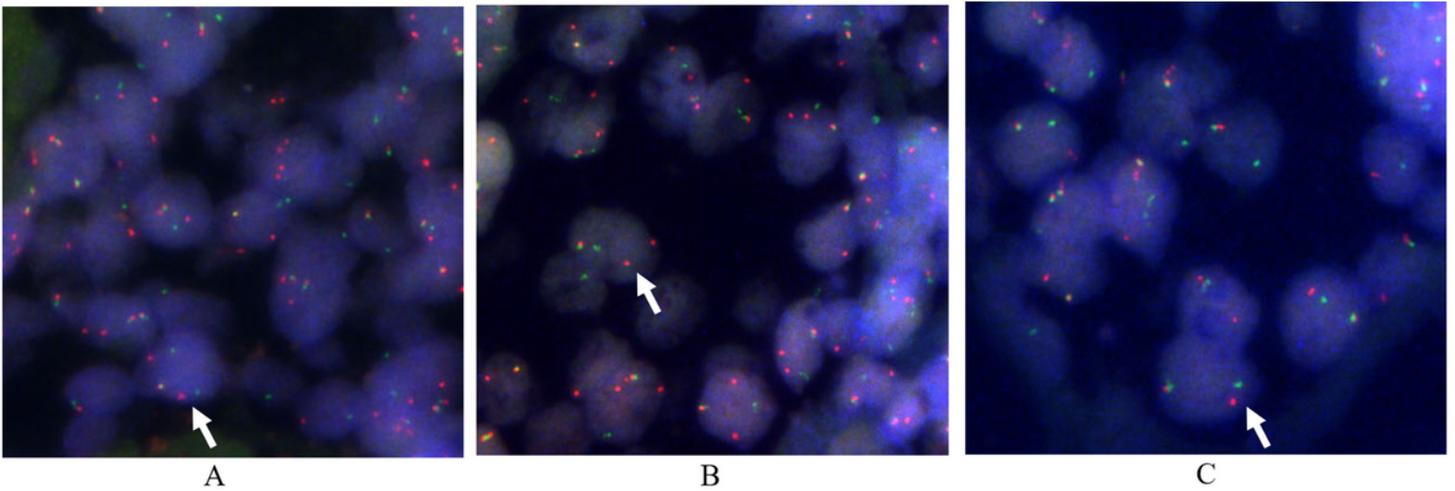
The authors declared that they have no competing interests.

## References

1. Storti S, Spina M, Pesce E, et al.: Rituximab plus bendamustine as front-line treatment in frail elderly (> 70 years) patients with diffuse large B-cell non-Hodgkin lymphoma: a phase II multicenter study of the Fondazione Italiana Linfomi. *HAEMATOLOGICA* 2018; 103(8): 1345-1350. DOI: 10.3324/haematol.2017.186569.
2. Swerdlow SH, Campo E, Pileri SA, et al.: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; 127(20): 2375-90. DOI: 10.1182/blood-2016-01-643569.
3. Scott DW, King RL, Staiger AM, et al.: High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with diffuse large B-cell lymphoma morphology. *Blood* 2018; 131(18): 2060-2064. DOI: 10.1182/blood-2017-12-820605.
4. Laude M, Lebras L, Sesques P, et al.: First-line treatment of double-hit and triple-hit lymphomas: Survival and tolerance data from a retrospective multicenter French study. *American journal of hematology* 2021; 96(3): 302-311. DOI: 10.1002/ajh.26068.
5. Klapper W, Kreuz M, Kohler CW, et al.: Patient age at diagnosis is associated with the molecular characteristics of diffuse large B-cell lymphoma. *Blood* 2012; 119(8): 1882-7. DOI: 10.1182/blood-2011-10-388470.
6. Peyrade F, Jardin F, Thieblemont C, et al.: Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *The Lancet Oncology* 2011; 12(5): 460-468. DOI: 10.1016/S1470-2045(11)70069-9.
7. Zhang W, Li G, Ma Y, et al.: Reduced-dose EPOCH-R chemotherapy for elderly patients with advanced stage diffuse large B cell lymphoma. *Annals of Hematology* 2018; 97(10): 1809-1816. DOI: 10.1007/s00277-018-3369-7.
8. Pfreundschuh M, Trümper L, Kloess M, et al.: Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL., vol 104, 2004; 634-41. DOI: 10.1182/blood-2003-06-2095.
9. Pinnix CC, Andraos TY, Dabaja B, et al.: Diffuse large B-cell lymphoma in very elderly patients over 80 years old: Incorporating consolidative radiation therapy into management decisions. *Advances in Radiation Oncology* 2017; 2(3): 370-380. DOI: 10.1016/j.adro.2017.04.004.
10. Sonnevi K, Wästerlid T, Melén CM, Harrysson S, Smedby KE, Wahlin BE: Survival of very elderly patients with diffuse large B-cell lymphoma according to treatment intensity in the immunochemotherapy era: a Swedish Lymphoma Register study. *British journal of haematology* 2021; 192(1): 75–81. DOI: 10.1111/bjh.16737.
11. Tucci A, Martelli M, Rigacci L, et al.: Comprehensive geriatric assessment is an essential tool to support treatmentdecisions in elderly patients with diffuse large B-cell lymphoma: a

- prospectivemulticenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL). *Leukemia & lymphoma* 2015; 56(4): 921-6. DOI: 10.3109/10428194.2014.953142.
12. Merli F, Luminari S, Tucci A, et al.: Simplified Geriatric Assessment in Older Patients With Diffuse Large B-Cell Lymphoma: The Prospective Elderly Project of the Fondazione Italiana Linfomi. *Journal of clinical oncology*, 2021;39(11):1214-1222. DOI: 10.1200/JCO.20.02465.
  13. Guido Gini MMTA: Lenalidomide and Rituximab (ReRi) As Front Line Chemo-Free Therapy of Elderly Frail Patients with Diffuse Large B-Cells Lymphoma. a Phase II Study of the Fondazione Italiana Linfomi (FIL). *Blood*. American Society of Hematology., vol 2020: *Blood* (2019) 134 (Supplement\_1): 2880. DOI: 10.1182/blood-2019-126568.
  14. Younes A, Sehn LH, Johnson P, et al.: Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma., *J Clin Oncol*. 2019;37(15):1285-1295. DOI: 10.1200/JCO.18.02403.
  15. Oberic L, Peyrade F, Puyade M, et al.: Subcutaneous Rituximab-MiniCHOP Compared With Subcutaneous Rituximab-MiniCHOP Plus Lenalidomide in Diffuse Large B-Cell Lymphoma for Patients Age 80 Years or Older. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 2021;39(11):1203-1213. DOI: 10.1200/JCO.20.02666.
  16. Schmitz R, Wright GW, Huang DW, et al.: Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *The New England journal of medicine* 2018; 378(15): 1396-1407. DOI: 10.1056/NEJMoa1801445.
  17. Al-Juhaishi T, Mckay J, Sindel A, Yazbeck V: Perspectives on chemotherapy for the management of double-hit lymphoma. *Expert opinion on pharmacotherapy* 2020; 21(6): 653-661. DOI: 10.1080/14656566.2020.1727445.
  18. Zeng D, Desai A, Yan F, et al.: Challenges and Opportunities for High-grade B-Cell Lymphoma With MYC and BCL2 and/or BCL6 Rearrangement (Double-hit Lymphoma). *American journal of clinical oncology* 2019; 42(3): 304-316. DOI: 10.1097/COC.0000000000000427.
  19. Locke FL, Ghobadi A, Jacobson CA, et al.: Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *The Lancet Oncology* 2019; 20(1): 31-42. DOI: 10.1016/S1470-2045(18)30864-7.
  20. Neelapu SS, Jacobson CA, Oluwole OO, et al.: Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood* 2020; 135(23): 2106-2109. DOI: 10.1182/blood.2019004162.

## Figures



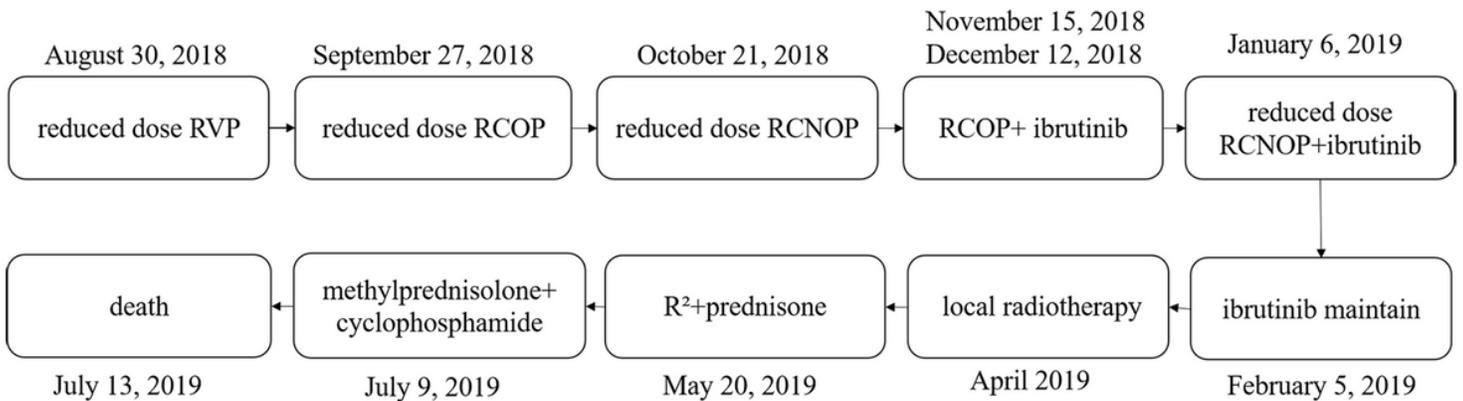
**Figure 1.** Fluorescent in-suit hybridization(FISH) examination of this patient. **A.** MYC gene rearrangement is positive; **B.** BCL6 gene rearrangement is positive; **C.** BCL2 gene rearrangement is positive. (normal cells have two yellow fusion signals in the cell; cells with positive gene rearrangement have orange-red and green separation signals in the cell (the white arrow as an example).

**Figure 1**

See image above for figure legend

**Figure 2**

See image above for figure legend



**Figure 3.** Treatment procedure of this patient. RVP(rituximab, vindesine, hydroprednisone), RCOP(rituximab, cyclophosphamide, vindesine, hydroprednisone), RCNOP(rituximab, cyclophosphamide, mitoxantrone, vindesine, prednisone), R<sup>2</sup> (rituximab, lenalidomide)

**Figure 3**

See image above for figure legend