Non-Hodgkin’s lymphoma in an elderly patient with renal dysfunction: a case report

Cong Ma1,*, Bingxiang Yu1,*, Haomin Zhang2, Bo Yang2, Dongwan Li2, Rong Li1 and Xuechun Lu2

Abstract
Objective: This study was performed to examine the treatment regimen used for an elderly patient with diffuse large B-cell lymphoma (DLBCL) complicated with renal dysfunction.
Case report: An 85-year-old man presented with nasal and sinus disorders in May 2018. He was also found to have renal insufficiency caused by long-term consumption of compound aminopyrine phenacetin tablets. Physical examination revealed irritation of the nasal mucous membrane on the right side and dark red nasal passages with a smooth surface. The right side of the neck contained several small peanut-sized lymph nodes. A biopsy of the right nasal neoplasm revealed germinal center type DLBCL. The mini–rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone regimen (mini-R-CHOP) was administered as the main chemotherapy regimen. Additionally, the use of thrombopoietin prevented further deterioration in renal function. This individualized treatment program helped the patient to achieve complete remission. The creatinine level decreased and was well maintained.
Conclusion: The mini-R-CHOP and rituximab cross-use regimen was found to be safe in an elderly patient with chronic renal insufficiency. Thrombopoietin exerted a protective effect on renal function.

Keywords
Diffuse large B-cell lymphoma, elderly patients, renal dysfunction, mini-R-CHOP, chemotherapy, thrombopoietin

Date received: 20 March 2020; accepted: 8 July 2020
Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL) in the elderly population, with an incidence rate of about 30% to 40%. The median age at onset is about 60 to 70 years; 50% of patients are aged more than 60 years, while about 40% of patients are aged more than 70 years. The incidence of NHL increases with age and has doubled in the last two decades.

The incidence of adverse reactions to chemotherapy increases with age because of the weak immune system in the elderly, leading to a poor prognosis and high mortality rate in older patients with NHL. Although treatment can result in remission, the long-term survival rate is low. Maartense et al. showed that among patients with NHL, the survival rate was significantly lower in those aged >70 than <70 years. The 5-year survival rate of patients aged 80 to 85 years and >85 years was 15% and 8%, respectively.

Elderly patients with DLBCL are a heterogeneous group, and treatment is based mainly on anthracycline chemotherapy drugs. Despite certain efficacy, the treatment is greatly influenced by morphological characteristics, immune phenotypes, genetics, and biology, and many patients do not achieve complete or partial remission and are prone to relapse. The combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is considered the standard treatment for DLBCL. However, the treatment of elderly patients remains challenging. Many elderly patients have renal insufficiency, especially at advanced ages. Renal function is a main factor that limits the standard dose of chemotherapy and affects the prognosis, but no specific prevention or treatment is currently available. This study was performed to examine the treatment of an elderly patient with NHL complicated with renal dysfunction. Thrombopoietin (TPO) was used to prevent the deterioration of renal function, and complete remission was achieved with an individualized treatment program.

Case presentation

The study protocol was approved by the ethics committees of the Second Medical Center and National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, Beijing. The participant provided written informed consent.

An 85-year-old Chinese Han man was diagnosed with DLBCL; 23 days later (25 June 2018), he was admitted to the Department of Health Medicine of PLA General Hospital. He was found to have nasal and sinus disorders in May 2018. Positron emission tomography/computed tomography (PET-CT) examination outside the hospital revealed foci of increased metabolic activity on the right side of the frontal sinus, ethmoid sinus, and maxillary sinus and in the nasal cavity. Further, multiple lymph nodes with increased metabolic activity were present on the right side of the neck and bilateral supraclavicular fossae. Hence, malignant lesions were considered. A nasal biopsy was performed, and the postoperative pathological examination revealed right nasal DLBCL (germinal center type). The immunohistochemical results were as follows: AE1/AE3 (−), Ki-67 index (70%), p53 (−), CD3 (scattered +), CD2 (+), CD10 (+), Bcl-6 (+), cyclin D1 (−), and Mum-1 (−). The result of Epstein–Barr virus-encoded RNA in situ hybridization was negative, and the patient was diagnosed with NHL. He also had renal insufficiency due to long-term use of compound aminopyrine phenacetin tablets,
and his serum creatinine level was 143 μmol/L. Physical examination revealed irritation of the nasal mucous membrane on the right side and dark red nasal passages with a smooth surface. Multiple hard peanut-sized lymph nodes were palpated on the right side of the neck; these were diagnosed as DLBCL. The patient and his family members refused a lumbar puncture and cerebrospinal fluid examination. An individualized treatment plan was developed according to the patient’s advanced age and renal insufficiency, and TPO (15,000 IU) was administered after each chemotherapy cycle. The first cycle of R-COP chemotherapy was performed in the hospital in July 2018. On 24 July 2018, the second cycle of mini-R-CHOP chemotherapy was performed. After the treatment, no obvious abnormally enlarged lymph nodes were found in the neck or bilateral supraclavicular fossae. The mini-R-CHOP plan was implemented on 14 August 2018 and rituximab was given once in the fourth cycle because of bladder inflammation. The fifth cycle of the mini-R-CHOP program was launched on 9 October 2018. TPO was administered after each of the aforementioned cycles. A systemic PET-CT examination on 15 October 2018 revealed the following: (1) thickening of the left nasal mucosa and a slight increase in metabolism, which we anticipated might change after the treatment (the complete molecular response score was 1–2); (2) increased metabolism on the left side of the nasopharynx, which we considered might be due to nonspecific uptake or inflammation; and (3) right maxillary sinus and ethmoid sinusitis. The detailed treatment plan is shown in Table 1 (the patient agreed to receive the aforementioned treatment and provided written informed consent).

Imaging, routine blood testing, and renal function changes before and after treatment

Comparison of PET-CT imaging before and after treatment

The patient’s physical examination in the hospital revealed irritation of the right nasal mucosa and dark red nasal passages with a smooth surface. Multiple hard peanut-sized lymph nodes were palpated on the right side of the neck. Before the second chemotherapy cycle, no enlarged superficial lymph nodes were found throughout the body, and the nasal mucosa was neither hyperemic nor edematous. No new microorganisms were seen in the middle nasal tract. The patient’s clinical symptoms and signs disappeared. The PET-CT findings were compared before and after the treatment (Figures 1 and 2, respectively).

Changes in routine blood parameters during treatment

The patient had good tolerance to chemotherapy. No obvious indications of bone marrow suppression were seen except for a slight decrease in the total number of white blood cells on 16 July and 23 August. After each TPO administration, the platelet count increased to different degrees, but the hemoglobin and white blood cell count were not significantly affected (Table 2 and Figure 3).

Changes in creatinine and urea nitrogen levels after TPO administration

The patient had a history of renal insufficiency caused by long-term use of pain-relieving tablets. After each TPO administration, the creatinine and urea nitrogen
levels decreased and then increased until the next TPO administration (Table 3 and Figure 4).

**Discussion**

Chronic renal insufficiency is a common disease among the elderly population. The incidence of renal insufficiency increases gradually with age. Survey data show that the prevalence of chronic kidney disease in patients aged less than 60 years, more than 60 years, and more than 75 years is approximately 10%, 20%, and 50%, respectively. Further, 11% of elderly patients aged more than 65 years

| Cycles                        | Treatment plan and time                                                                                                                                                                                                 | Adverse effects                      |
|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| First cycle                   | Rituximab 600 mg by pump (day 1)  
(2 July 2018)  
R-COP  
Cyclophosphamide 600 mg by intravenous drip (day 2)  
Vindesine 4 mg by intravenous drip (day 2)  
Prednisone 60 mg by oral administration (days 2–7) | Myelosuppression, level 2  
Digestive tract reaction, level 0 |
| Second cycle                  | Rituximab 600 mg by pump (day 1)  
(24 July 2018)  
mini-R-CHOP  
Cyclophosphamide 600 mg by intravenous drip (day 2)  
Vindesine 4 mg by intravenous drip (day 2)  
Doxorubicin hydrochloride liposome injection 40 mg by intravenous drip (day 2)  
Prednisone 60 mg (days 3–6), then gradually reduced and stopped | Myelosuppression, level 0  
Digestive tract reaction, level 0 |
| Third cycle                   | Rituximab 600 mg by pump (day 1)  
(14 August 2018)  
mini-R-CHOP  
Cyclophosphamide 600 mg by intravenous drip (day 2)  
Vindesine 4 mg by intravenous drip (day 2)  
Doxorubicin hydrochloride liposome injection 20 mg by intravenous drip (day 2)  
Prednisone 60 mg (days 3–6), then gradually reduced and stopped | Myelosuppression, level 0  
Digestive tract reaction, level 0 |
| Fourth cycle                  | Rituximab 600 mg by pump (day 1)  
(10 September 2018)  
mini-R-CHOP  
Cyclophosphamide 600 mg by intravenous drip (day 2)  
Vindesine 4 mg by intravenous injection (day 2)  
Doxorubicin hydrochloride liposome injection 20 mg by intravenous drip (day 2)  
Prednisone 60 mg (days 3–6), then gradually reduced and stopped | Myelosuppression, level 0  
Digestive tract reaction, level 0 |
| Fifth cycle                   | Rituximab 600 mg by pump (day 1)  
(9 October 2018)  
mini-R-CHOP  
Cyclophosphamide 600 mg by intravenous drip (day 2)  
Vindesine 4 mg by intravenous injection (day 2)  
Doxorubicin hydrochloride liposome injection 20 mg by intravenous drip (day 2)  
Prednisone 60 mg (days 3–6), then gradually reduced and stopped | Myelosuppression, level 0  
Digestive tract reaction, level 0 |
| Sixth cycle                   | Rituximab 600 mg by pump (day 1)  
(30 October 2018)  
mini-R-CHOP  | Myelosuppression, level 0  
Digestive tract reaction, level 0 |
without diabetes or high blood pressure have at least stage 3 renal disease. Renal insufficiency has become the bottleneck of clinical drug use and treatment for elderly patients, especially those of very advanced age. While treating elderly patients with chronic renal insufficiency, the treatment plan should be reasonably

**Figure 1.** Positron emission tomography–computed tomography report from Peking Union Medical College Hospital on 5 June 2018, before treatment. A soft tissue density shadow was seen in the right frontal sinus, ethmoid sinus, maxillary sinus, and nasal cavity, with increased radioactive uptake. The standardized uptake value was 20.4, and the shadow was invading the right orbit. The radioactivity uptake increased on the right side of the neck (areas I, II, III, and V) and supraclavicular fossae. The size of the shadow was 0.4 to 1.0 cm, and the maximum standardized uptake value was 1.7 to 8.1.

**Figure 2.** Positron emission tomography–computed tomography report of PLA General Hospital on 15 October 2018, after treatment. The soft tissue density shadow had disappeared from the right frontal sinus, ethmoid sinus, maxillary sinus, and nasal cavity. The previously observed increased radioactivity uptake was not seen on the right side of the neck (areas I, II, III, and V) or in the supraclavicular fossae. The left nasal mucosa was thickened, and the metabolic activity in this area was slightly increased. The complete metabolic response score was 1 to 2.
chosen with consideration of various factors.

The present report described an 85-year-old patient with DLBCL. Despite his good general condition, the patient had chronic renal insufficiency due to long-term use of compound aminopyrine phenacetin tablets. A detailed assessment was performed before the treatment according to the European Society for Medical Oncology Clinical Practice Guidelines, and a comprehensive geriatric assessment was also performed. The patient could not tolerate the standard dose of R-CHOP chemotherapy; therefore, he required either a reduced dose or progressive therapy. R-COP was adopted in the first cycle, and mini-R-CHOP and rituximab cross-use treatment was given on the basis that the renal function did not worsen after chemotherapy with the goal of achieving complete remission.

TPO was administered at the end of each cycle of chemotherapy. After each TPO administration, the patient’s renal function (creatinine and urea nitrogen levels) showed a relatively obvious downward trend and then gradually increased until TPO was administered again after the next cycle of chemotherapy. Therefore, we speculated that TPO might have had a protective effect on renal function in this patient with senile lymphoma. A renal protective function of TPO has not been reported in previous clinical studies, but relevant basic and animal experiments have been conducted. TPO has been found to promote the expression of immediate early gene X-1 (IEX-1) and its related pathways, scavenge free radicals, and promote repair of

| Time             | Hemoglobin (g/L) | White blood cell count ($\times 10^9$/L) | Platelet count ($\times 10^9$/L) |
|------------------|------------------|------------------------------------------|---------------------------------|
| 26 June 2018     | 109              | 4.16                                     | 274                             |
| 2 July 2018      | 106              | 3.44                                     | 248                             |
| 9 July 2018      | 92               | 5.70                                     | 265                             |
| 16 July 2018     | 115              | 2.63                                     | 263                             |
| 23 July 2018 with TPO | 121          | 5.84                                     | 291                             |
| 27 July 2018     | 105              | 5.00                                     | 234                             |
| 31 July 2018     | 106              | 4.61                                     | 331                             |
| 13 August 2018   | 115              | 3.18                                     | 274                             |
| 14 August 2018 with TPO | 106          | 4.75                                     | 245                             |
| 17 August 2018   | 112              | 2.20                                     | 382                             |
| 23 August 2018   | 119              | 7.22                                     | 347                             |
| 7 September 2018 | 112              | 6.32                                     | 267                             |
| 10 September 2018| 112              | 5.54                                     | 253                             |
| 8 October 2018   | 113              | 4.17                                     | 211                             |
| 9 October 2018 with TPO | 106        | 7.71                                     | 225                             |
| 15 October 2018  | 112              | 5.38                                     | 225                             |
| 29 October 2018  | 116              | 5.38                                     | 225                             |
| 30 October 2018 with TPO | 107        | 4.48                                     | 195                             |
| 1 November 2018  | 107              | 4.48                                     | 195                             |
DNA damage.\textsuperscript{11–13} Wang et al.\textsuperscript{14} confirmed that TPO could promote hematopoietic stem cell regeneration in rats treated with radiotherapy and that TPO administration before radiotherapy could reduce hematopoietic stem cell damage and mutagenesis in mice. DNA damage repair occurred via the DNA–protein kinase-dependent pathway.\textsuperscript{15}

Our patient’s renal function was stable, and his creatinine level was lower than that during his first admission. We conclude that the mini-R-CHOP and rituximab cross-use regimen was relatively safe for this elderly patient with chronic renal insufficiency. TPO combined with chemotherapy may have a protective effect on renal function; however, its clinical mechanism needs further exploration.

**Ethics**

The study protocol was approved by the ethics committees of the Second Medical Center and National Clinical Research Center for Geriatric Diseases, Chinese
**Table 3.** Changes in creatinine and urea nitrogen levels during thrombopoietin treatment.

| Time                        | Creatinine (µmol/L) | Urea nitrogen (mmol/L) |
|-----------------------------|---------------------|------------------------|
| 26 June 2018                | 142                 | 9.2                    |
| 2 July 2018                 | 128                 | 10.0                   |
| 9 July 2018                 | 121                 | 9.9                    |
| 16 July 2018                | 147                 | 10.0                   |
| 23 July 2018 with TPO       | 123                 | 9.9                    |
| 27 July 2018                | 110                 | 10.1                   |
| 31 July 2018                | 114                 | 9.4                    |
| 13 August 2018              | 161                 | 10.0                   |
| 14 August 2018 with TPO     | 108                 | 7.3                    |
| 17 August 2018              | 122                 | 8.4                    |
| 3 September 2018            | 167                 | 10.4                   |
| 7 September 2018            | 159                 | 9.1                    |
| 10 September 2018           | 152                 | 9.9                    |
| 8 October 2018              | 133                 | 9.3                    |
| 9 October 2018 with TPO     | 118                 | 8.1                    |
| 15 October 2018             | 145                 | 8.5                    |
| 30 October 2018 with TPO    | 127                 | 6.4                    |

**Figure 4.** Changes in renal function (creatinine and urea nitrogen) after thrombopoietin treatment.
PLA General Hospital, Beijing. The participant provided written informed consent.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

**Funding**

This study was supported by the Bidding Project of the National Center for Clinical Medicine of Geriatric Diseases in 2017 (NCRCG-PLAGH-2017011) and the Translational Medicine Project of PLA General Hospital (2017TM-020).

**ORCID iD**

Xuechun Lu  https://orcid.org/0000-0002-9768-4087

**References**

1. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood* 2010; 116: 3724–3734.
2. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d’Etude des Lymphomes de l’Adulte. *J Clin Oncol* 2005; 23: 4117–4126.
3. Nabhan C, Smith SM, Helenowski I, et al. Analysis of very elderly (>80 years) non-Hodgkin lymphoma: impact of functional status and co-morbidities on outcome. *Br J Haematol* 2012; 156: 196–204.
4. Fisher SG and Fisher RI. The epidemiology of non-Hodgkin’s lymphoma. *Oncogene* 2004; 23: 6524–6534.
5. Maartense E, Kluin-Nelemans HC, Le Cessie S, et al. Different age limits for elderly patients with indolent and aggressive non-Hodgkin lymphoma and the role of relative survival with increasing age. *Cancer* 2000; 89: 2667–2676.
6. Cencini E, Fabbri A, Guerrini S, et al. Long-term remission in a case of plasmablastic lymphoma treated with COMP (cyclophosphamide, liposomal doxorubicin, vincristine, prednisone) and bortezomib. *Eur J Haematol* 2016; 96: 650–654.
7. Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003; 41: 1–12.
8. Moccia AA and Thieblemont C. Curing diffuse large B-cell lymphomas in elderly patients. *Eur J Intern Med* 2018; 58: 14–21.
9. Vitolo U, Seymour JF, Martelli M, et al. Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; 27: v91–v102.
10. Tucci A, Martelli M, Rigacci L, et al. Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL). *Leuk Lymphoma* 2015; 56: 921–926.
11. Hirao A. TPO signal for stem cell genomic integrity. *Blood* 2014; 123: 459–460.
12. Hamelin V, Letourneux C, Romeo PH, et al. Thrombopoietin regulates IEX-1 gene expression through ERK-induced AML1 phosphorylation. *Blood* 2006; 107: 3106–3113.
13. De Laval B, Pawlikowska P, Barbieri D, et al. Thrombopoietin promotes NHEJ DNA repair in hematopoietic stem cells through specific activation of Erk and NF-kappaB pathways and their target, IEX-1. *Blood* 2014; 123: 509–519.
14. Wang C, Zhang B, Wang S, et al. Recombinant human thrombopoietin promotes hematopoietic reconstruction after severe whole body irradiation. *Sci Rep* 2015; 5: 12993.
15. De Laval B, Pawlikowska P, Petit-Cocault L, et al. Thrombopoietin-increased DNA-PK-dependent DNA repair limits hematopoietic stem and progenitor cell mutagenesis in response to DNA damage. *Cell Stem Cell* 2013; 12: 37–48.