Successful treatment of non-Hodgkin’s lymphoma with rituximab and dose-adjusted CHOP therapy in a patient with concomitant end-stage renal disease requiring haemodialysis

Noriaki Kawano¹, Naoko Yokota-Ikeda¹,*, Sayaka Kawano¹, Shuro Yoshida¹, Kiyoshi Yamashita¹, Keiko Kodama¹, Shigehiro Uezono¹, Yoshiya Shimao², Fumiko Kawano³ and Akira Ueda¹

¹Department of Internal Medicine, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan, ²Department of Pathology, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan and ³Faculty of Letters, University of Keio, Tokyo, Japan

Correspondence and offprint requests to: Noriaki Kawano; E-mail: kawanoriaki@yahoo.co.jp

*Naoko Yokota-Ikeda is the equally contributed author.

Abstract
Although malignancy is a fatal complication of end-stage renal disease (ESRD) requiring haemodialysis, successful treatment of haematological malignancies has been rarely reported. We describe the case of a 64-year-old man who presented with non-Hodgkin’s lymphoma (NHL; clinical stage, IVB) concomitant with ESRD. Before chemotherapy, haemodialysis was initiated, and one course of dose-adjusted CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) therapy followed by eight courses of rituximab therapy were administered according to the performance status and degree of organ dysfunction. Consequently, the patient was disease free for 27 months. Thus, rituximab plus CHOP combination therapy was effective for NHL concomitant with ESRD.

Keywords: end-stage renal disease; haemodialysis; non-Hodgkin’s lymphoma; rituximab and dose-adjusted CHOP therapy

Case report
A 64-year-old man presenting with a painful tumour of the right orbita was referred to a regional hospital on 22 February 2007. He had been diagnosed with diabetes mellitus when he was 50 years old, and coronary artery bypass graft surgery for 3-vessel coronary disease had been performed on 20 October 2006. On admission, the patient was normotensive (blood pressure, 146/62 mmHg; heart rate, 72 beats/min). Physical examination revealed tumours of the right orbita, left cervical lymph nodes and right inguinal lymph nodes. The laboratory findings are summarized in Table 1.

A fluorodeoxyglucose-positron emission tomography/computed tomography scan showed extranodal lesions in the right orbita, lung and testis as well as the cervical, thoracic, abdominal and inguinal lymph nodes (Figure 1A). Histological analysis of lymph node specimens showed diffuse expansion and infiltration of abnormal lymphoid cells (Figure 1B). Flow cytometric and immunohistochemical analysis of the lymph node specimens revealed that the surface marker was positive for CD19, CD20, CD25, MUM1, bcl2 and λ chain (Figure 1C). On the basis of all these findings, we finally diagnosed NHL [diffuse large B-cell lymphoma; clinical stage (CS) IVB]. The patient was classified as a high-risk patient according to the international prognostic index (IPI) for NHL [6] because of the following findings: age > 60 years, CS > III, performance...
status > 2, number of extranodal lesions > 2 and lactate dehydrogenase levels > normal.

Prior to chemotherapy, haemodialysis was initiated because of ESRD. Subsequently, we administered an adjusted dose of CHOP (25 mg/m² doxorubicin on Day 1, 1.4 mg/m² vincristine on Day 1, 375 mg/m² cyclophosphamide on Day 1 and 60 mg/m² prednisolone for 5 days) to control the activity of NHL (Figure 2). After undergoing one course of CHOP with haemodialysis, the patient attained complete response (CR) with resolution of systemic lymphadenopathy and extranodal lesions. A psoas haematoma developed during chemotherapy. When the psoas haematoma occurred, due to the administration of warfarin against atrial fibrillation, we changed the anticoagulant agent from warfarin to heparin during haemodialysis without progression of psoas haematoma. Red blood cell concentrate (RCC) transfusions have been necessary when first chemotherapy of CHOP therapy was performed because of the combination of chemotherapy and haemodialysis that can cause blood spoil at every session.

Although the patient was at high risk for survival according to IPI, we selected rituximab chemotherapy because the

Table 1. Laboratory findings on admission

| Urinalysis          | Coagulation          | Serology         |
|---------------------|----------------------|------------------|
| Protein             | PT (s)               | CRP              |
| Sugar               | APTT (s)             | HTLV-I           |
| Occult Blood pH     | Fib                  | sIL-2R           |
|                     | FDP                  | 61200 IU/l       |
| Peripheral cell count |                     | HbA1C            |
| WBC                 | T.Bil                | 0.23 mg/dL       |
| STAB                | AST                  | 18 IU/L          |
| SEG                 | ALT                  | 12 IU/L          |
| LYMPH               | LDH                  | 996 IU/L         |
| MONO                | γ-GTP                | 17 IU/L          |
| EOSIN               | Na                   | 138 mEq/dL       |
| BASO                | Glu                  | 201 mg/dL        |
| Abnormally          | K                    | 4.87 mEq/dL      |
| RBC                 | Cl                   | 106 mEq/dL       |
| Hb                  | Ca                   | 7.9 mg/dL        |
| Hct                 | BUN                  | 66.8 mg/dL       |
| MCV                 | Cr                   | 7.4 mg/dL        |
| MCH                 | UA                   | 9.9 mg/dL        |
| PLT                 | Ferritin             | 690 ng/mL        |
| Ret                 | ALB                  | 4.3 g/dL         |

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin concentration; Plt, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; Fib, fibrinogen; FDP, fibrin/fibrinogen degradation products; T.Bil, total bilirubin; AST, aspartate aminotransferase; ALT: alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, gamma-glutamyl transpeptidase; Cr, creatinine; TP, total protein; ALB, albumin; CRP, c-reactive protein; HTLV-I, human T-cell leukemia virus type I; sIL-2R, soluble interleukin 2 receptorR; HbA1C, hemoglobin A1c.

Fig. 1. (A) Fluorodeoxyglucose-positron emission tomography/computed tomography scan showing the cervical, thoracic, abdominal and inguinal lymph nodes and extranodal lesions in the right orbits, lung and testis. (B) Histological findings showing diffuse expansion and infiltration of abnormal lymphoid cells. (C) Immunohistological findings showing expansion of CD20-positive abnormal lymphoid cells.
patient showed slight improvement in performance status from 3 to 2 despite treatment and rehabilitation.

Subsequently, the patient was administered 375 mg/m² rituximab every week because rituximab is not eliminated by haemodialysis [2]. Rituximab was administered at a dose of 375 mg/m² with sodium chloride without any overhydration problems. After the administration of chemotherapy, the patient was still able to urinate with haemodialysis.

When the activity of NHL was under control, we established a blood access site for permanent haemodialysis. In addition, we administered four courses of rituximab every month. However a major concern with rituximab is the risk of severe bacterial, fungal infection and the development of progressive multifocal leukoencephalopathy, there were no major adverse events except psoas haematoma in our case. RCC transfusions have not been necessary when only rituximab treatment was administered. A monitoring of the B cells in the peripheral blood was not done during chemotherapy.

The patient maintained CR and did not require further treatment for NHL during the 27 months.

Discussion

According to a report of the Japanese Society for Dialysis Therapy, the fatal complications in ESRD patients undergoing haemodialysis are heart failure, infection and malignancy, accounting for 23.9, 20.8 and 9.4% deaths, respectively, among the 25,224 dialysis patients who died in 2009 [1]. Although most malignant tumours originate from the gastrointestinal tract (stomach and colon), kidneys, lungs and thyroid, haematological malignancies such as lymphomas have rarely been reported [1]. Maisonneuve et al. [7] reported that the incidence of NHL in patients undergoing dialysis was 0.5–2 times higher than that in healthy people. Although the incidence of malignancy tends to be high in patients undergoing haemodialysis, it is not clear whether haemodialysis itself increases the incidence of malignancy [1, 7, 8].

Rituximab plus CHOP combination therapy has been established as the first-line treatment for NHL [5]. To date, ESRD patients undergoing haemodialysis have not been successfully treated for NHL because of the insufficiency

![Clinical course](image)

Fig. 2. Clinical course of our patient.

| Table 2. Chemotherapy for NHL concomitant with ESRD requiring haemodialysis |
|---------------------------------------------------------------|
| Reference (year) | Age | Sex | Diagnosis | Clinical stage | Treatment | Chronic renal failure on dialysis | Side effect | Response |
| Jillella et al. (2002) | 54 | Male | Follicular lymphoma (Grade 1) | III | Rituximab 375 mg/m², 4 course | Haemodialysis (3 times per week) | Tumour lysis syndrome | CR |
| Feldmann et al. (2007) | 70 | Male | Diffuse large B-cell lymphoma | III | Rituximab (375 mg/m²) + CHOP 6 course (first course/second course: CPA, ADR, 50% dose) (3 course full dose) | Haemodialysis (3 times per week) | Hyperglycaemia | PR |
| Niscola et al. (2009) | 70 | Female | Splenic marginal zone lymphoma | IV | Rituximab 375 mg/m², 6 course: Chlorambucil (6 mg/m², Days 1–10), 6 course | Haemodialysis (n.d.) | - | CR |
| Present case | 66 | Male | Diffuse large B-cell lymphoma | IVB | CHOP 1 course, rituximab 375 mg/m², 8 course | Haemodialysis (3 times per week) | Psoas haematoma | CR, alive |

*n.d., not described; CR, complete response. Previously published reports on NHL patients with ESRD requiring haemodialysis and our patient who underwent combination therapy with rituximab and CHOP therapy.
in the drug dose caused by renal insufficiency and because of the risk of infection under immunocompetent conditions. The appropriate dosage and course of therapeutic agents for NHL concomitant with ESRD requiring haemodialysis have not yet been established. A few previous studies have reported that NHL concomitant with ESRD requiring haemodialysis was successfully treated with chemotherapy (Table 2). Treatment with a fractionated dose of rituximab or dose-adjusted CHOP therapy such as half-dose cyclophosphamide and doxorubicin was found to be effective [2–4]. In our case, we modified the dose of CHOP and administered a half dose of cyclophosphamide and doxorubicin and a full dose of vincristine and prednisolone without rituximab because the performance status of our patient was 3 and the risk of tumour lysis syndrome was high. During chemotherapy, psoas haematoma was the only complication observed in our patient because of the administration with warfarin. Jillella et al. [2] reported that rituximab was not eliminated via haemodialysis. Our patient was administered four courses of rituximab weekly and monthly to achieve a good outcome. However a major concern with rituximab is the risk of severe bacterial, fungal infection and the development of progressive multifocal leukoencephalopathy, there were no major adverse events except psoas haematoma in our case.

To the best of our knowledge, this is the first report of a patient who received rituximab plus dose-adjusted CHOP therapy for NHL concomitant with ESRD requiring haemodialysis, wherein haemodialysis was initiated at initial diagnosis. Our findings show that adjusting the dose of the drug and modifying therapy according to the performance status, degree of organ dysfunction and prognosis is safe, efficient and feasible.

In conclusion, the findings in our case suggested that rituximab plus dose-adjusted CHOP along with haemodialysis is effective for treating NHL concomitant with ESRD. A randomized prospective study on patients undergoing haemodialysis is required to further understand the incidence, histology, indications for treatment, therapeutic strategy and dosage and courses of chemotherapy for NHL in ESRD patients undergoing haemodialysis.

Conflict of interest statement. None declared.

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