Case Report

^{131}I-Rituximab Treatment in Patient with Relapsed Non-Hodgkin's Lymphoma: The First Case Report in Thailand

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Radioimmunotherapy (RIT) with ^{131}I-rituximab is a safe and effective treatment in patients with relapsed, refractory follicular lymphoma. The authors demonstrated the first case of ^{131}I-rituximab treatment in the patient with relapsed non-Hodgkin's lymphoma (NHL) in Thailand. There was no immediate complication after treatment. Impressive treatment response occurred.

Keywords: *^{131}I-rituximab, Non-Hodgkin's lymphoma, Radioimmunotherapy*

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Case Report

The authors demonstrated the first case of ^{131}I-rituximab treatment in the patient with relapsed Non-Hodgkin's lymphoma (NHL) in Thailand. ^{131}I-rituximab treatment is approved by Ethical Clearance Committee on Human Rights Related to Researchers Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

This woman had a history of follicular lymphoma in the right groin treated with chemotherapy since 2006. Clinical remission was achieved since then. In January 2012, she developed fever and a mass in the left lower quadrant abdomen. CT scan of the whole abdomen (Fig. 1) revealed matted enlarged lymphadenopathies along the left common iliac, external and internal iliac regions, measuring about 9.3x5.9 cm. Entrapment of the left distal ureter resulted in moderate left hydronephrosis.

She underwent fine needle aspiration at soft tissue mass in LLQ, which proved to be large cell transformation from low-grade lymphoma. She received four cycles of salvage chemotherapy between February and May 2012. A follow-up CT scan of the whole abdomen (Fig. 2) in June 2012 showed significantly decreased in the size of the large matted left external iliac lymphadenopathies, now measuring 2.4 cm in longest dimension. She was sent for ^{131}I-rituximab treatment in July 2012.

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^{131}I-rituximab preparation and radiolabelling

^{131}I-rituximab radiolabelling was done by the Thailand Institute of Nuclear Technology (TINT). All

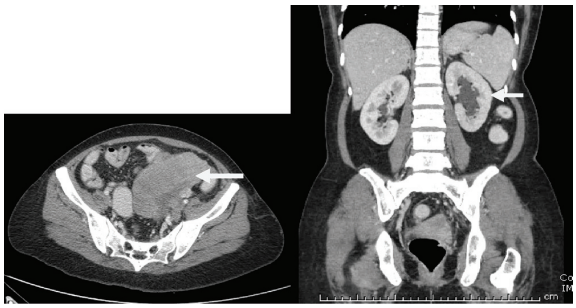

Fig. 1 CT scan of the patient in Jan 2012 showed large lymphadenopathies along the left common iliac, left and right iliac regions (left image) as well as left hydronephrosis (right image).

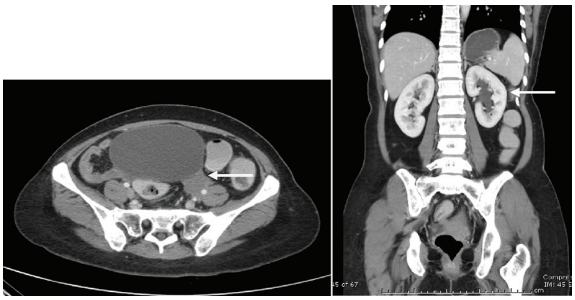

Fig. 2 A follow-up CT scan in June 2012 was done after salvage chemotherapy. There was significantly decreased in the size of matted lymph nodes (left image). Left hydronephrosis is still seen (right image).

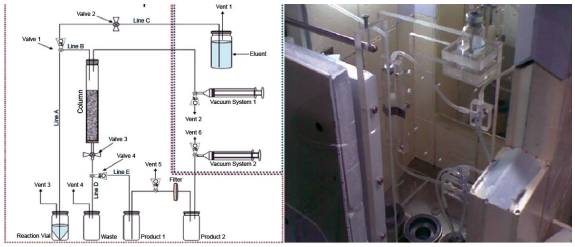

Fig. 3 Synthesis module for ^{131}I-rituximab (Radioisotope Center, TINT).

procedures were conducted in Grade C clean room. The synthesis module (Fig. 3) was placed in Grade A environment inside a Glove Box connected with HEPA filter, air circuiting system and exhaust duct. Lead shielding with sliding door was placed around module to protect the operator from the handling of high activity ^{131}I. The reagents, column, and silicone tubing were sterilized by autoclaving at 121°C for 20 minutes and the system was validated and tested for sterility, pyrogen, toxicity and radiation dose to operator.

Radiolabelling of ^{131}I-rituximab was done by Chloramine-T method described earlier by Turner JH et al[1]. Non-stabilized ^{131}I in V-shape vial was mixed with 200 µl 0.15 M Phosphate buffer, 10 mg of rituximab and 48 µl Chloramine-T. It was then incubated at room temperature for 60 seconds. The reaction was stopped by adding 60 µl Sodium metabisulfite. The reaction mixture was transferred to synthesis module and purified by Sephadex G-10 column by eluting the product with 0.01M PBS buffer pH 7.4, collected fraction 6-15 (1 ml/fraction) for product ^{131}I-rituximab. The purified product was sterilized by 0.22 µm filtration and dispensed for patient dose. Sample was taken for quality control by TLC and HPLC systems.

Treatment protocol and patients' specific dosimetry

The basic goal of radioimmunotherapy (RIT) is to administer the maximum treatment dose that would deliver optimal radiation absorbed dose to tumor tissue with minimal or acceptable toxicity to critical organs. The principle side effect of RIT is bone marrow suppression, especially thrombocytopenia and leukopenia[2]. Contribution of radiation absorbed dose to bone marrow should not exceed 2 Gy that is equivalent to 0.75 Gy of whole body absorbed dose[3,4]. Then, evaluation of bone marrow uptake before ^{131}I-rituximab treatment with a diagnostic dose of radioiodinated rituximab is a good predictor of bone marrow toxicity.

Treatment protocol

D0: 130 mg KI was given orally for thyroid blockage and continued for two weeks.

D1: 375 mg/m^2 rituximab was slowly infused at Hematology unit, Department of Medicine, Ramathibodi Hospital. Then, 185 MBq of ^{131}I-rituximab was injected intravenously.

D1-6: Total body images (Hawkeye 4 SPECT/CT, GE Healthcare) at 10 minutes, three and six days were used to determine the effective half-life of the radioiodinated antibody in the patient. Imaging was performed using HEGP (High Energy General Purpose) collimators with an energy window of 20% center at 364 keV for ^{131}I. A step mode moving the scanning bed of three minutes per step with the body contour turned off was used. The background count was performed with the same protocol as the whole-body imaging but used 60 seconds per step. It was made sure that the bed height, detectors height, patient position and any accessories (e.g. pillows) are all the same with each scan. After that, the equation of Wahl RL et al[5] was used to calculate the therapeutic dose of ^{131}I-rituximab.

D7: The patient was sent to Hematology unit for unlabeled rituximab. Then the patient was sent to Division of Nuclear Medicine for treatment dose of ^{131}I-rituximab. In this case, ^{131}I-rituximab 1,110 MBq was given intravenously.

D10-14: Total body scan (post treatment) was acquired.

Hospital course and follow-up

The authors carefully reviewed the patient's history to select the patient who might be getting the benefit of ^{131}I-rituximab treatment. This patient had a history of relapsed follicular lymphoma. She had residual lymphadenopathies after salvage

chemotherapy. She was doing well and physical examination was unremarkable. Complete blood count (CBC) of this patient before treatment was shown as follows: Hct 36%, WBC 4.57x10^3/cumm (PMN 57%, Lymphocyte 15% and others 28%), platelet 67x10^3/cumm. Most common side effect of RIT is bone marrow suppression. The authors decided to precede ^{131}I-rituximab at about six to eight weeks after the last cycle of chemotherapy, although her CBC was abnormal. The authors already discussed with the patient about possible complications that may occur after treatment. Calculated ^{131}I-rituximab treatment dose in this patient was 1,110 MBq.

The patient was admitted at Ramathibodi Hospital for a night. There was no immediate complication. However, the patient developed febrile neutropenia at a week after the treatment, which is not common. Bone marrow suppression usually occurred at four to six weeks after RIT. Pulmonary as pergillosis was clinically diagnosed. After antifungal treatment, clinical and imaging were improved.

Post treatment total body scan (Fig. 4) was obtained three days after 1,110 MBq of ^{131}I-rituximab injection. There was no SPECT/CT image due to gamma camera out of order at that time. Although there was no obviously increased uptake on post treatment scan, radiographic evidence of treatment response occurred.

A follow-up CT abdomen at three months after ^{131}I-rituximab treatment (Fig. 5) revealed no residual lymphadenopathy, resulting in resolving left hydronephrosis. There was only ^{131}I-rituximab treatment in between CT scan in Fig. 3 and 5.

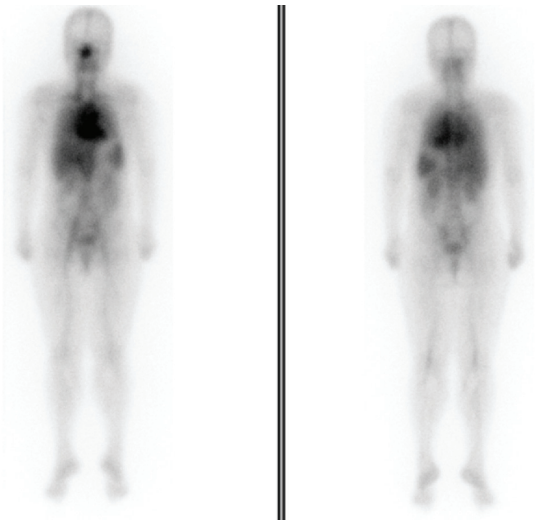

Fig. 4 Post treatment total body scan after ^{131}I-rituximab treatment did not show an obvious lesion on planar image. There was no SPECT/CT image due to the SPECT/CT gamma camera out of order at that time.

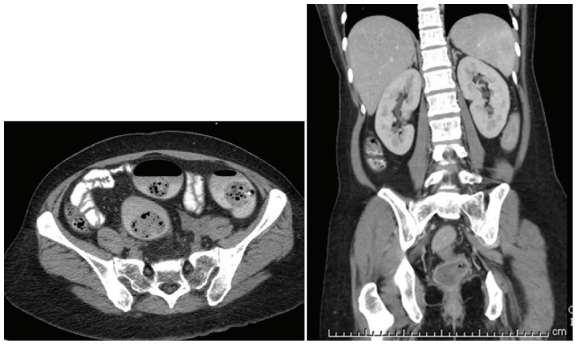

Fig. 5 A follow-up CT scan in Oct 2012 (3 months after ^{131}I-rituximab revealed no residual lymphadenopathy. Resolving left hydronephrosis is observed.

Discussion

Radioimmunotherapy (RIT) with an anti-CD20 monoclonal antibody (Mab) conjugated to a beta-emitting radioisotope is a safe and effective treatment in patients with relapsed, refractoryfollicular lymphoma[6-8]. It has been proved in many articles that RIT is safe[9,10], well tolerated and produces higher ORR and CR compared with rituximab alone[11]. Two widely commercial available radiopharmaceuticals, ^{90}Y-Zevalin and ^{131}I-Bexxar, are approved by the FDA. There are some advantages of ^{90}Y-Zevalin over ^{131}I-Bexxar. Firstly, dosimetry is not required. Treatment dose of ^{90}Y-Zevalin is easily calculated based on the patient's platelet. ^{90}Y is a pure beta emitter radioisotope, therefore, the patient can be treated as an OPD case.

The authors have had experience treating a few cases of ^{90}Y-Zevalin in the past. Appreciable treatment responses occurred. However, the cost is very expensive and cannot be reimbursed from the government. The patients need to pay by themselves. Most of the patients cannot afford the cost of RIT.

Recently, sporadic usage of ^{131}I-rituximab treatment has been reported in Europe[12], and Australia[1,13-15]. Leahy MF et al[13] reported overall response rate (ORR) of 76%, with 53% attaining a complete response (CR) or CR unconfirmed (CRu), which is comparable with ^{90}Y-Zevalin. Repeated ^{131}I-rituximab treatment was also recently reported[14,15]. Staffs from Ramathibodi Hospital had a fortunate opportunity to visit Prof. Harvey Turner at Fremantle Hospital, Australia to learn about ^{131}I-rituximab preparation and treatment. To initiate this treatment in

the hospital, a good collaboration between nuclear medicine staff, hematologists, and radiopharmacists from TINT is very important. The authors have the first case report of the feasibility and efficacy of ^{131}I-rituximab treatment at Ramathibodi Hospital. Although there was no obviously abnormal increase of ^{131}I-rituximab uptake seen on planar image, impressive treatment response occurred. The authors plan to have more cases of ^{131}I-rituximab treatment in the future.

In conclusion, the authors demonstrated the first case of ^{131}I-rituximab treatment from Ramathibodi Hospital. To the best of our knowledge, this is the first case of ^{131}I-rituximab in Thailand. TINT provides in-house radio labelling ^{131}I-rituximab. ^{131}I-rituximab is a safe and effective treatment in relapsed follicular lymphoma. Impressive treatment response occurred in the presented patient. However, validation in more numbers of patients may be warranted.

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The authors wish to thank Prof. Harvey Turner for his hospitality while the authors visited Fremantle hospital and many helpful discussions on initiating ^{131}I-rituximab in Thailand. The authors kindly appreciate the Radioisotope Center, TINT for ^{131}I-rituximab preparation.

Potential conflicts of interest

None.

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การใช้สารเภสัชรังสี 131I-rituximab รักษาผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's lymphoma ที่กลับเป็นซ้ำ: รายงานผู้ป่วยรายแรกในประเทศไทย

อาภากร โฆษิตวัฒนฤกษ์, วิโรจน์ ช่างม่วง, จตุพล แสงสุริยัน, กิตติพงษ์ ทองกล่ำ, ชนิกา ศรีธรา, จิรวัฒน์ อุตตมะกุล, วิชชนา จำรูญรัตน์, คนึงนิจ ธรรมนิรัติ, ยชญ์ อนงค์พรยศกุล, สุภร จันทร์จารุณี

Radioimmunotherapy ถือเป็นการรักษาที่ปลอดภัยและมีประสิทธิภาพ สำหรับผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's lymphoma ที่มีการกลับเป็นซ้ำ คณะผู้นิพนธ์รายงานการใช้สารเภสัชรังสี ^{131}I-rituximab รักษาสำหรับผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's lymphoma ที่มีการกลับเป็นซ้ำ โดยเป็นผู้ป่วยรายแรกในประเทศไทยที่ได้รับการรักษาด้วยสารเภสัชรังสี 131I-rituximab หลังจากได้รับการรักษาไม่มีผลข้างเคียงทันที และผลการรักษาเป็นที่น่าพอใจ