Radioimmunotherapy with ^{131}I -Rituximab in a Patient with Diffuse Large B-Cell Lymphoma Relapsed After Treatment with ^{90}Y -Ibritumomab Tiuxetan

Geon Wook Kang · Hye Jin Kang · Dong-Yeop Shin ·
Ha Ra Gu · Hong Seok Choi · Sang Moo Lim

Received: 26 May 2013 / Revised: 1 August 2013 / Accepted: 13 August 2013 / Published online: 30 August 2013
© Korean Society of Nuclear Medicine 2013

Abstract We report a case that demonstrates the efficacy of radioimmunotherapy (RIT) with radioiodinated rituximab (^{131}I -rituximab) for relapsed diffuse large B-cell lymphoma (DLBCL). A 79-year-old male patient with DLBCL initially achieved a complete response (CR) after six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) therapy. However, the lymphoma relapsed 20 months later. Although the patient had achieved a second and a third CR after two cycles of ^{90}Y -ibritumomab tiuxetan, he experienced a third relapse approximately 3 years later. Between March and June 2011, the patient received three cycles of ^{131}I -rituximab. Although he had achieved partial response after the second cycle, the disease progressed after the third cycle, and the total progression-free survival was thus 5 months. The patient suffered only relatively mild toxicity (grade 1 thrombocytopenia) during treatment. RIT with ^{131}I -rituximab is therefore potentially effective in patients with relapsed DLBCL, even after the failure of ^{90}Y -ibritumomab tiuxetan therapy.

Keywords ^{131}I -rituximab · Rituximab · Radioimmunotherapy · Diffuse large B-cell lymphoma · Refractory

Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent subtypes of non-Hodgkin lymphoma (NHL) worldwide [1]. Significant improvements in the outcome of patients with DLBCL have been achieved with the incorporation of rituximab into standard chemotherapeutic regimens. Although gene expression analyses revealed the biological heterogeneity of DLBCL, CD20-targeted therapy has been proved to be effective. Fu et al. reported that additional rituximab was effective in both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of DLBCL [2].

The goal of radioimmunotherapy (RIT) is to target tumors more effectively while sparing normal cells by using a radiolabeled monoclonal antibody (mab). There are two commercially available anti-CD20 antibodies for treating patients with relapsed NHL, one was radiolabeled with yttrium-90 (^{90}Y -ibritumomab tiuxetan; Zevalin; Biogen Idec, Inc., San Diego, CA, and Schering AG, Berlin, Germany) and the other was radiolabeled with iodine-131 (^{131}I -tositumomab; Bexxar; Corixa Corp., Seattle, WA). These radioimmunotherapeutic agents have resulted in promising outcomes for the overall response rate of up to 80 % and prolonged response duration of more than 1 year [3, 4]. Turner et al. reported a similar response when RIT was performed using ^{131}I -rituximab, with an overall response rate of 76 % (high CR or unconfirmed CR rate of 53 %) after a single treatment with ^{131}I -rituximab in a total of 91 patients with relapsed or refractory NHL [5]. However, the efficacy of ^{131}I -rituximab treatment after the failure of RIT with ^{90}Y -ibritumomab tiuxetan or ^{131}I -tositumomab has not yet been reported.

Here, we report a case in which RIT using ^{131}I -rituximab was used to treat a patient with DLBCL who had relapsed after ^{90}Y -ibritumomab tiuxetan treatment.

G. W. Kang · H. J. Kang (✉) · D.-Y. Shin · H. R. Gu · H. S. Choi
Department of Internal Medicine, Korea Cancer Center Hospital,
Korea Institute of Radiological and Medical Sciences, 75 Nowon-gil,
Nowon-gu, Seoul 139-706, Republic of Korea
e-mail: mdhyejin@gmail.com

S. M. Lim
Department of Nuclear Medicine, Korea Cancer Center Hospital,
Korea Institute of Radiological and Medical Sciences,
Seoul, South Korea

Case Report

A 79-year-old male patient was admitted to an outside hospital because of a left upper neck mass. After excisional biopsy, he was diagnosed with CD20-positive DLBCL in May 2005. Immunohistochemistry results indicated that the mass was positive for leucocyte common antigen, CD20 and CD79a and negative for cytokeratins, CD15, CD30 and anaplastic lymphoma kinase 1. Involvement of the left cervical level II lymph node and each of the lower paratracheal, preaortic and right hilar lymph nodes was noted. However, bone marrow involvement was not detected. The patient had diabetes mellitus, hypertension and coronary heart disease and had undergone percutaneous coronary intervention at the mid-left anterior descending artery in June 2003. He had no relevant family history or drinking behavior. However, he was a heavy smoker.

The patient had achieved CR after six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) therapy, which was initiated in May 2005. However, he was diagnosed with relapsed DLBCL in 2007. At that time, positron emission tomography-computed tomography (PET-CT) showed lymphoma involvement in the left lower cervical lymph node, the left internal mammary node, both axillary nodes, both lower paratracheal nodes, the aortopulmonary window, the paraaortic node, the left internal mammary node, the subcarinal node, both hilar nodes, right interlobar lymph nodes and the spleen. Although the patient achieved a second CR after one cycle of ^{90}Y -ibritumomab tiuxetan in March 2007, he experienced a second relapse. He then achieved a third CR after retreatment with ^{90}Y -ibritumomab tiuxetan in April 2008.

However, in February 2011, the patient experienced a third relapse in the left neck level II, mediastinal, axillary, left gastric, peripancreatic, portocaval, paraaortic, left external iliac and inguinal lymph nodes, and in both lungs, as shown in Fig. 1a. At this point, he was referred to our institution to discuss the possibility of enrolling in an ongoing phase II trial of RIT with ^{131}I -rituximab for relapsed/refractory NHL. However, he was older than the maximum age criterion for the trial; thus, he was administered ^{131}I -rituximab as part of the group outside of the clinical trial. Although he was not considered part of the clinical trial, treatment was administered in accordance with the predefined study protocol [6]. Before infusing the unlabeled rituximab, potassium iodine was administered to prevent thyroid uptake of ^{131}I at least 24 h before RIT. He received unlabeled rituximab (70 mg) intravenously for 5 min in the radiation isolation room, followed by the therapeutic dose (7400 MBq, 200 mCi) of ^{131}I -labeled rituximab intravenously for 15 min. During treatment, we monitored the patient's heart and respiratory rates and performed electrocardiography.

The toxicity experienced by the patient was principally hematological (grade 1 thrombocytopenia). His laboratory

results before the first cycle of ^{131}I -rituximab were as follows: white blood cell count, $4820/\mu\text{l}$, hemoglobin level, 11.9 g/dl and platelet count, $150 \times 10^9/\text{l}$. His platelet count had fallen to $103 \times 10^9/\text{l}$ just before the second cycle of ^{131}I -rituximab, but during the first day of that cycle, it fell to its lowest value of $86 \times 10^9/\text{l}$. The time to platelet nadir was thus 7 weeks.

Figure 1 shows the serial images of ^{18}F -fludeoxyglucose PET-CT for the patient. He had achieved partial response (PR) after one cycle of ^{131}I -rituximab treatment in March 2011 (Fig. 1b) and showed sustained PR after the second cycle of ^{131}I -rituximab in April 2011. After two cycles of ^{131}I -rituximab, a PET-CT scan showed that the uptake in the hypermetabolic lesions of both lungs had decreased (standard uptake value: 1.5), and no other hypermetabolic lesions were observed (Fig. 1c). However, the patient experienced progression after the third cycle of ^{131}I -rituximab in July 2011. After three cycles of ^{131}I -rituximab, PET-CT revealed two focal hypermetabolic lymph nodes in the left inguinal area (Fig. 1d).

The progression-free survival of the patient was thus 5 months. He was treated with external beam radiation therapy directed to the left inguinal lymph node. After 25 fractions of radiation therapy (total radiation dose 45 Gy), he had achieved CR and was then treated with oral cyclophosphamide between December 2011 and July 2012. There has been no evidence of recurrence up to March 2013 (Fig. 1e).

Discussion

RIT has emerged as a promising treatment option for patients with refractory or relapsed lymphoma. One of the first radioimmunotherapeutic drugs, ^{90}Y -ibritumomab tiuxetan was approved by the US Food and Drug Administration (FDA) in 2002 for the treatment of patients with relapsed or refractory low-grade or follicular B-cell NHL, including patients with rituximab refractory follicular NHL. Another radioimmunotherapeutic drug, ^{131}I -tositumomab, was approved a year later for the treatment of patients with CD20 positive, low-grade, follicular or transformed NHL, whose disease is refractory to rituximab. In addition, ^{90}Y -ibritumomab tiuxetan is used in the front-line setting following a CR or a PR to induction chemotherapy.

Although ^{131}I -rituximab has not been approved, it is administered for relapsed/refractory NHL in the clinical trial setting, and it has shown promising results to date [5]. Kang et al. also reported that single RIT with ^{131}I -rituximab gave a modest response (29 %; 7 of 24 patients) among Korean patients with relapsed/refractory B-cell NHL [6].

Despite RIT having been used to successfully treat patients with indolent NHL, there have been only a few studies on its use in patients with DLBCL. Morschhauser et al. reported that ^{90}Y -ibritumomab tiuxetan used as a second-line therapy for

Fig. 1 Serial images of ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography after administration of ^{131}I -rituximab showing (a) relapsed diffuse large B-cell lymphoma at baseline, with involvement of both lungs and multiple lymph nodes (left neck level II, mediastinum, axillary, left gastric, peripancreatic, portocaval, paraaortic, left external iliac and inguinal area); b marked regression of lymphoma in both lungs and

multiple lymph nodes after treatment with one cycle of ^{131}I -rituximab; c slight regression of lymphoma in both lungs after the second cycle of ^{131}I -rituximab; d disease progression in the left inguinal area 1 month after completing the third cycle of ^{131}I -rituximab; (e) sustained complete response of lymphoma in the left inguinal area after external beam radiation therapy directed to the left inguinal lymph node

patients with relapsed DLBCL who had previously been treated with R-CHOP as a first-line therapy contributed to an overall response rate of 23 % (3 of 13 patients) [7]. ^{90}Y -ibritumomab has also been evaluated as a post-remission therapy in high-risk patients [8] or elderly patients with DLBCL [9, 10]. However, the use of ^{90}Y -ibritumomab as a consolidation treatment for DLBCL remains controversial.

^{131}I -tositumomab has mainly been studied as a part of a conditioning regimen for autologous hematopoietic stem cell transplantation for relapsed DLBCL. This includes a recent phase III study in which the progression-free survival and overall survival of patients treated with a ^{131}I -tositumomab-containing conditioning regimen were not significantly different compared to that of those treated with a rituximab-containing regimen [11].

Despite these advances, the use of ^{131}I -rituximab as a basis for the RIT of DLBCL has not been widely studied thus far. Furthermore, there have been no reports on RIT using ^{131}I -rituximab after RIT with commercial conjugates such as ^{90}Y -ibritumomab or ^{131}I -tositumomab has failed in refractory DLBCL. Here, we have described the case of a relapsed patient with DLBCL who had been treated with rituximab-based chemotherapy (R-CHOP) as a first-line treatment and was subsequently treated with ^{90}Y -ibritumomab tiuxetan as a second-line therapy, and then had a partial response with ^{131}I -rituximab as a third-line treatment. Kaminski et al. reported that re-treatment with ^{131}I -tositumomab following a previous response can produce a second responses in 94 % (30 of 32) patients [12]. Furthermore, Kang et al. reported that repeated treatment of ^{131}I -rituximab before progression, after a single treatment with ^{131}I -rituximab, increased the response rate among patients with relapsed or refractory B cell NHL compared with only a single treatment [68 (21 of 31 patients) vs. 29 %] [13].

Based on the findings of Kaminski et al., our patient was treated with ^{90}Y -ibritumomab tiuxetan following the first and second relapses after R-CHOP therapy. However, after the third relapse, he could not receive further treatment using ^{90}Y -ibritumomab tiuxetan because of its high cost. Therefore, for the next RIT, he was treated with ^{131}I -rituximab.

With respect to toxicity, ^{131}I -rituximab is a tolerable option for patients with relapsed/refractory B-cell NHL. A previous study by Michael et al. found that the toxicity of ^{131}I -rituximab in a total of 142 patients with lymphoma was mainly self-limited myelosuppression, with grade 4 thrombocytopenia and grade 4 neutropenia in 6 % and 10 % of cases, respectively [14]. The only toxicity observed in our patient was a grade 1 thrombocytopenia, without anemia and neutropenia. The time to the platelet nadir was 7 weeks. When the PET-CT scan revealed high uptake by the inguinal lymph nodes after the third treatment with ^{131}I -rituximab, suggesting progressive disease, we decided not to perform tissue diagnosis because of his old age, heart problem and ongoing palliation. However, there is still a possibility that a high uptake by inguinal lymph nodes could be due to benign lesions rather than true progression, given the disease course after subsequent local radiation therapy and oral chemotherapy.

Despite a limitation, our case is noteworthy as it suggests that ^{131}I -rituximab results in only acceptable toxicity and is a possible salvage therapy after the failure of RIT using commercial conjugates such as ^{90}Y -ibritumomab tiuxetan or ^{131}I -tositumomab in patients with DLBCL.

Further prospective studies are needed to evaluate the efficacy of ^{131}I -rituximab and to compare the efficacy of different sequentially applied radioimmunotherapeutic drugs for patients with DLBCL.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

- Jaffe ES. The 2008 WHO classification of lymphomas: Implications for clinical practice and translational research. *Hematol Am Soc Hematol Educ Program*. 2009;523–31.
- Fu K, Weisenburger DD, Choi WW, Perry KD, Smith LM, Shi X, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. *J Clin Oncol*. 2008;26:4587–94.
- Kaminski MS, Zelenetz AD, Press OW, Saleh M, Leonard J, Fehrenbacher L, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-hodgkin's lymphomas. *J Clin Oncol*. 2001;19:3918–2.
- Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-hodgkin's lymphoma. *J Clin Oncol*. 2002;20:2453–6.
- Leahy MF, Seymour JF, Hicks RJ, Turner JH. Multicenter phase II clinical study of iodine-131-rituximab radioimmunotherapy in relapsed or refractory indolent non-hodgkin's lymphoma. *J Clin Oncol*. 2006;24:4418–25.
- Kang HJ, Lee SS, Kim KM, Choi TH, Cheon GJ, Kim WS, et al. Radioimmunotherapy with (131)I-rituximab for patients with relapsed/refractory B-cell non-hodgkin's lymphoma (NHL). *Asia Pac J Clin Oncol*. 2011;7:136–45.
- Morschhauser F, Illidge T, Huglo D, Martinelli G, Paganelli G, Zinzani PL, et al. Efficacy and safety of yttrium-90 ibritumomab tiuxetan in patients with relapsed or refractory diffuse large B-cell lymphoma not appropriate for autologous stem-cell transplantation. *Blood*. 2007;110:54–8.
- Han EJ, Lee SE, Kim SH, Sohn HS, Jung SE, Park G, et al. Clinical outcomes of post-remission therapy using (90)yttrium ibritumomab tiuxetan (zevalin(R)) for high-risk patients with diffuse large B-cell lymphoma. *Ann Hematol*. 2011;90:1075–82.
- Zinzani PL, Tani M, Fanti S, Stefoni V, Musuraca G, Castellucci P, et al. A phase II trial of CHOP chemotherapy followed by yttrium 90 ibritumomab tiuxetan (zevalin) for previously untreated elderly diffuse large B-cell lymphoma patients. *Ann Oncol*. 2008;19:769–73.
- Zinzani PL, Rossi G, Franceschetti S, Botto B, Di Rocco A, Cabras MG, et al. Phase II trial of short-course R-CHOP followed by 90Y-ibritumomab tiuxetan in previously untreated high-risk elderly diffuse large B-cell lymphoma patients. *Clin Cancer Res*. 2010;16:3998–4004.
- Vose JM, Carter S, Burns LJ, Ayala E, Press OW, Moskowitz CH, et al. Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: Results from the BMT CTN 0401 trial. *J Clin Oncol*. 2013;31:1662–8.
- Kaminski MS, Radford JA, Gregory SA, Leonard JP, Knox SJ, Kroll S, et al. Re-treatment with I-131 tositumomab in patients with non-hodgkin's lymphoma who had previously responded to I-131 tositumomab. *J Clin Oncol*. 2005;23:7985–93.
- Kang HJ, Lee SS, Byun BH, Kim KM, Lim I, Choi CW, et al. Repeated radioimmunotherapy with 131I-rituximab for patients with low-grade and aggressive relapsed or refractory B cell non-hodgkin lymphoma. *Cancer Chemother Pharmacol*. 2013;71:945–53.
- Leahy MF, Turner JH. Radioimmunotherapy of relapsed indolent non-hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. *Blood*. 2011;117:45–52.