Safety of $^{90}$Y-ibritumomab Tiuxetan Treatment for Japanese Patients in Real-world Clinical Practice

Hiroshi Yoshikawa,* Hiroshi Sakurashita, Satoru Izumitani, Takanori Taogoshi, Yasuyuki Saeki, and Hiroaki Matsuo

Department of Pharmaceutical Services, Hiroshima University Hospital; 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan.

(Received May 18, 2018; Accepted September 1, 2018)

When undergoing $^{90}$Y-ibritumomab tiuxetan ($^{90}$Y-IT) treatment, patients are discharged from hospital soon after initiation of treatment and followed up as outpatients. Thus it is important to apprise patients of the safety information regarding $^{90}$Y-IT treatment. However, studies investigating the safety of $^{90}$Y-IT in real-world clinical practice are lacking. We sought to investigate the adverse events arising from $^{90}$Y-IT administration to patients in our hospital. Patients who received $^{90}$Y-IT treatment at Hiroshima University Hospital from April 2010 to December 2014 were eligible for this study. The medical records of the patients were reviewed retrospectively. Eleven patients (median age, 65 years) were enrolled. Patients were classified into 3 groups according to the number of prior regimens: 1, 2–3, or $>3$, consisting of 5, 4, and 2 patients, respectively. The number of patients with induced grade 3 and 4 hematotoxicity, respectively, was 5 and 0 for leukocytopenia, 3 and 2 for neutropenia, and 3 and 2 for thrombocytopenia. The median nadir time was 37 d for leukocytopenia, 37 d for neutropenia, 36 d for thrombocytopenia, and 43 d for anemia. Patients with 2 or more prior regimens tended to experience grade 3 or 4 hematotoxicity more frequently than those with 1 prior regimen. In conclusion, we showed that hematotoxicity is a major adverse event of $^{90}$Y-IT treatment and that the nadir time is later than that with conventional anticancer agents. Medical staff, including pharmacists, should direct attention to the initial symptoms of hematotoxicity, especially in those patients who have received several prior regimens.

Key words—ibritumomab tiuxetan; adverse event; hematotoxicity; number of prior regimen

INTRODUCTION

Yttrium-90 ($^{90}$Y)-labeled ibritumomab tiuxetan ($^{90}$Y-IT) has been approved for the treatment of CD20-positive recurrent or refractory low-grade B-cell non-Hodgkin lymphoma and mantle cell lymphoma. By labeling the anti-CD20 monoclonal antibody, ibritumomab, with the radioisotope $^{90}$Y, the isotope is accumulated in the CD20-positive B-cell tumor as a target cell, and the beta rays from $^{90}$Y and the complement-dependent cytotoxic action after binding to the monoclonal antibody leads to an antitumor effect.1) A phase II clinical trial in Japan revealed that $^{90}$Y-IT was effective for recurrent or refractory low-grade B-cell non-Hodgkin lymphoma, with a response rate of 83% and a complete remission rate of 68%.2)

Hiroshima University (HU) Hospital has been dispensing $^{90}$Y-IT treatment since 2010. In HU Hospital most patients who undergo $^{90}$Y-IT treatment are discharged a few days after starting $^{90}$Y-IT administration and are followed up via outpatient care. For this reason, it is extremely important to provide advance information to patients about the frequency and timeline of adverse events. Hematotoxicity, headache, gastrointestinal symptoms, and fatigue have been reported as adverse events of $^{90}$Y-IT treatment, although only few medical institutions conduct this therapy and the number of real-world reports is limited,3,4) particularly in Japan. In this study, we investigated the adverse events in patients treated with $^{90}$Y-IT in our hospital.

METHODS

Patients who received $^{90}$Y-IT treatment at HU Hospital from April 2010 to December 2014 were eligible. We excluded cases for which we could not collect patient information because of transfer to another hospital after $^{90}$Y-IT treatment.

Adverse events after $^{90}$Y-IT administration were evaluated retrospectively through medical records. Lowest values of leukocytes, neutrophils, hemoglobin, and platelets, in addition to days after administration were used to investigate the extent...
Table 1. Patients Characteristics and Hematotoxicity

| No. | Age (year) | Sex | Lymphoma subtype | Number of prior regimens | Supportive therapy | Baseline platelet count (× 10^3/mm^3) | Hematotoxicity Grade |
|-----|------------|-----|-------------------|--------------------------|--------------------|----------------------------------------|----------------------|
| 1   | 65         | F   | FL                | 10                       |                    | 115                                    | Leukocytopenia 3 | Neutropenia 3 | Thrombocytopenia 3 |
| 2   | 49         | F   | FL                | 4                        | G-CSF, PT          | 149                                    | Leukocytopenia 3 | Neutropenia 3 | Thrombocytopenia 4 |
| 3   | 72         | F   | MALT              | 1                        |                    | 274                                    | Leukocytopenia 2 | Neutropenia 1 | Thrombocytopenia 0 |
| 4   | 60         | M   | FL                | 2                        |                    | 198                                    | Leukocytopenia 2 | Neutropenia 2 | Thrombocytopenia 2 |
| 5   | 46         | F   | others            | 2                        | G-CSF, PT          | 162                                    | Leukocytopenia 3 | Neutropenia 4 | Thrombocytopenia 4 |
| 6   | 72         | M   | FL                | 1                        | G-CSF              | 213                                    | Leukocytopenia 3 | Neutropenia 4 | Thrombocytopenia 3 |
| 7   | 87         | F   | FL                | 3                        | G-CSF              | 259                                    | Leukocytopenia 2 | Neutropenia 3 | Thrombocytopenia 2 |
| 8   | 84         | F   | FL                | 1                        | G-CSF              | 194                                    | Leukocytopenia 2 | Neutropenia 2 | Thrombocytopenia 2 |
| 9   | 55         | M   | MALT              | 1                        |                    | 163                                    | Leukocytopenia 2 | Neutropenia 1 | Thrombocytopenia 2 |
| 10  | 53         | F   | MALT              | 3                        | G-CSF              | 108                                    | Leukocytopenia 3 | Neutropenia 2 | Thrombocytopenia 3 |
| 11  | 73         | M   | MALT              | 1                        | G-CSF              | 279                                    | Leukocytopenia 2 | Neutropenia 2 | Thrombocytopenia 2 |

Febrile neutropenia was found in only one case. Granulocyte-colony stimulating factor and platelet transfusion were administered in 7 cases and 2 cases, respectively. FL: follicular lymphoma, MALT: mucosa associated lymphoid tissue, G-CSF: granulocyte-colony stimulating factor, PT: platelet transfusion.

Table 2. Severity and Nadir of Hematotoxicity

| Hematotoxicity [nadir, median (range)] | Number of patients |
|----------------------------------------|--------------------|
| Leukocytopenia [37 (7–52) d]           |                    |
| Grade 3                                | 5 (45.5%)          |
| Grade 4                                | 0                  |
| Neutropenia [37 (7–52) d]              |                    |
| Grade 3                                | 3 (27.3%)          |
| Grade 4                                | 2 (18.2%)          |
| Thrombocytopenia [36 (16–44) d]        |                    |
| Grade 3                                | 3 (27.3%)          |
| Grade 4                                | 2 (18.2%)          |
| Anemia [43 (11–62) d]                  |                    |
| Grade 3                                | 0                  |
| Grade 4                                | 0                  |

RESULTS AND DISCUSSION

Eleven patients were enrolled in the study. Patients’ profiles and the numbers of prior regimens are summarized in Table 1. Some studies have reported that the number of prior regimens is related to hematotoxicity severity. After 90Y-IT administration, 9 patients achieved complete remission and 1 gained partial remission, while the outcome of the remaining patient was unknown.

The numbers of patients with grade 3 and 4 hematotoxicity were 5 and 0 for leukocytopenia, 3 and 2 for neutropenia, and 3 and 2 for thrombocytopenia, respectively. Median nadir times for leukocytopenia, neutropenia, thrombocytopenia and anemia were 37 d, 37 d, 36 d and 43 d, respectively (Tables 1 and 2). Febrile neutropenia was found in only one case. Granulocyte-colony stimulating factor (G-CSF) and platelet transfusion were administered in 7 and 2 cases, respectively. G-CSF was administered for therapeutic purpose when Grade ≥ 3 leukopenia or neutropenia occurred, or their counts reached nadir. The median number of days to G-CSF administration was 36 d. The relation between the number of prior regimens and the grade of leukocytopenia or thrombocytopenia showed a moderate correlation whereas neutropenia showed a weak correlation, although neither were significant (Fig. 1). There was no significant difference in hematotoxicity.
Fig. 1. Correlation between the Number of Prior Regimen and the Hematotoxicity Grade

Table 3. Summary of Hematotoxicity after 90Y-ibritumomab Tiuxetan Treatment

|                | Leukocytopenia | Neutropenia | Thrombocytopenia |
|----------------|----------------|-------------|-----------------|
|                | Grade < 3 | Grade ≥ 3 | p-value | Grade < 3 | Grade ≥ 3 | p-value | Grade < 3 | Grade ≥ 3 | p-value |
| Age (year)     | n      | n          |         | n      | n          |         | n      | n          |         |
| < 65 (n = 5)   | 2      | 3          | 0.39    | 2      | 2          | 0.60    | 1      | 3          | 0.26    |
| ≥ 65 (n = 6)   | 4      | 2          |         | 3      | 3          |         | 4      | 2          |         |
| Sex            | n      | n          |         | n      | n          |         | n      | n          |         |
| male (n = 3)   | 2      | 1          | 0.58    | 2      | 1          | 0.58    | 2      | 1          | 0.58    |
| female (n = 8) | 4      | 4          |         | 4      | 4          |         | 4      | 4          |         |
| Number of prior regimen | n     | n          |         | n      | n          |         | n      | n          |         |
| 1 (n = 5)      | 4      | 1          | 0.18    | 4      | 1          | 0.18    | 4      | 1          | 0.18    |
| ≥ 2 (n = 6)    | 2      | 4          |         | 2      | 4          |         | 2      | 4          |         |

Fisher’s exact probability test. p-value for the differences in hematotoxicity of Grade ≥ 3 according to age (<65 vs. ≥ 65), sex (male vs. female), number of prior regimen (1 vs. ≥ 2).

Hematotoxicity of Grade ≥ 3 according to sex (male vs. female), age (≥ 65 vs. < 65), and number of prior regimens (1 vs. ≥ 2). However, patients who received 2 or more prior regimens tended to suffer hematotoxicity of Grade ≥ 3 compared with those who received only 1 prior regimen (Table 3). Four patients had Grade 1 non-hematologic toxicity, and the symptoms were nausea, malaise, dyspepsia, and epigastric pain, respectively. Marginal elevation of LDH was found in one case. Hypoalbuminemia and bilirubin, AST, ALT elevation was not observed.

In this study, adverse events of Grade ≥ 3 leukocytopenia, neutropenia, and thrombocytopenia were observed in 45% of patients after 90Y-IT treatment. The median time to reach nadir after 90Y-IT treatment was longer than for other cytotoxic anticancer agents (7–14 d). In phase II studies in Japanese patients, hematotoxicity of Grade ≥ 3 was evident in approximately 70% of patients. In this study, the ratio of developing hematotoxicity of Grade ≥ 3 was lower than previously reported, which may be explained by the difference in the number of prior regimens. The ratio of patients who had undergone more than 3 regimens was 33% in the domestic phase II study, compared with 18% in the present study. It was reported by Emmanouilides et
that the number of patients with Grade 4 hematotoxicity increased in proportion to the number of prior regimens.\textsuperscript{5} A relationship between the number of prior regimens and thrombocytopenia has also been described.\textsuperscript{4,6} These results indicate that the number of prior regimens affects the severity of hematotoxicity. Therefore, the expression ratio of hematologic toxicity of Grade \( \geq 3 \) is considered to be low in this study because about 50\% of patients had received one prior regimen. Moderate correlations between the number of prior regimens and severity of leukocytopenia or thrombocytopenia were observed. Thus, we compared the frequency of Grade \( \geq 3 \) hematotoxicity between patients with 1 and at least 2 prior regimens, whereby there was a tendency that hematologic toxicity of Grade \( \geq 3 \) was more severe in patients with 2 or more prior regimens. These results suggest the necessity of paying particular attention to hematotoxicity in patients with multiple prior regimens. In addition, it has been reported that the response rate to 90Y-IT treatment is significantly higher in Japanese cases with fewer prior regimens,\textsuperscript{2,7} suggesting that earlier introduction of 90Y-IT treatment is warranted to obtain optimal therapeutic effect and prevention of adverse events.

In conclusion, we showed that in patients undergoing 90Y-IT treatment, hematotoxicity is a major adverse event that is expressed later in comparison with other cytotoxic anticancer agents. Moreover, in patients with more than 2 prior regimens there is a possibility of more severe hematotoxicity. These data mostly support the previous results reported among Japanese patients. Therefore, it is important that for safe utilization of 90Y-IT the pharmacist should provide appropriate information, such as the timeline of adverse events and corresponding fever and infection, to physicians and patients. Pharmacists should also check the number of prior regimens, and suggest to clinicians to follow-up patients more frequently for safe use of 90Y-IT in case patients multiple prior regimens have been implemented.

\textbf{Conflict of Interest} No conflict of interest to be disclosed.

\textbf{REFERENCES}

1) Alcindor T., Witzig T. E., \textit{Curr. Treat. Options Oncol.}, 3, 275–282 (2002).
2) Tobinai K., Watanabe T., Ogura M., Morishima Y., Hotta T., Ishizawa K., Itoh K., Okamoto S., Taniwaki M., Tsukamoto N., Okumura H., Terauchi T., Nawano S., Matsusako M., Matsuno Y., Nakamura S., Mori S., Ohashi Y., Hayashi M., Endo K., \textit{Cancer Sci.}, 100, 158–164 (2009).
3) Nakagawa M., Uike N., Choi I., Hayashi T., Uehara S., \textit{Jpn. J. Radiol.}, 30, 642–647 (2012).
4) Hayashi T., Abe M., Shimizu H., Okubo H., Nakagawa M., Uike N., Tomizawa T., \textit{J. Jpn. Soc. Hosp. Pharm.}, 46, 959–962 (2010).
5) Emmanouilides C., \textit{J. Clin. Exp. Hematopathol.}, 47, 43–60 (2007).
6) Witzig T. E., White C. A., Gordon L. I., Wiseman G. A., Emmanouilides C., Murray J. L., Lister J., Multani P. S., \textit{J. Clin. Oncol.}, 21, 1263–1270 (2003).
7) Uike N., Choi I., Tsuda M., Haji S., Toyoda K., Suehiro Y., Abe Y., Hayashi T., Sawamoto H., Kaneko K., Shimokawa M., Nakagawa M., \textit{Int. J. Hematol.}, 100, 386–392 (2014).