LETTER TO THE EDITOR

Monthly administration of rituximab is useful for patients with ocular adnexal mucosa-associated lymphoid tissue lymphoma

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Ocular adnexal mucosa-associated lymphoid tissue-type lymphoma (OAL) is a distinct category of indolent B-cell non-Hodgkin’s lymphoma.\(^1\) OAL is commonly found in clinical stage IE or IIE at diagnosis, and is associated with a favorable prognosis.\(^2-5\) However, patients often require treatment because of cosmetic problems, discomfort or pain. Although local irradiation therapy has been frequently used as a treatment option for OAL, it is associated with high risks of complications, such as dry eye, cataract, decreased visual acuity, conjunctivitis, conjunctival ulcer, retinopathy, optic neuropathy and cancer.\(^6-10\) The repeated administration of rituximab, weekly four times, is an effective alternative associated with high response rates and lower risks of complications. However, a high rate of relapse has reportedly been a marked concern with this modality.\(^2,11,12\) Accordingly, an optimal treatment strategy with fewer adverse effects and sustainable efficacy is required to treat patients with OAL because such patients show a more favorable prognosis. Here, we retrospectively compared the efficacy and adverse effects of the monthly administration of rituximab with that of radiotherapy as the initial treatment for OAL. We showed that monthly rituximab may be more useful in view of the better event-free survival (EFS) and fewer adverse effects on treating patients with OAL, compared with radiotherapy and weekly infusion four times of rituximab.

Table 1 shows the characteristics of patients diagnosed with OAL in our department between 2008 and 2013. Informed consent for each treatment was obtained from all patients. Responses were assessed by whole-body computed tomography, FDG-positron emission tomography, magnetic resonance imaging and ophthalmologic tests after the completion of eight cycles of rituximab monotherapy. Ten patients with OAL received rituximab alone at 375 mg/m\(^2\) per day intravenously every 4 weeks for up to eight cycles. Alternatively, seven OAL patients received local irradiation of a single eye or both eyes as a historical control in our hospital. As shown in Table 1, the median age was 70 (36–79 years) in the group treated with rituximab alone, and 73 (43–82 years) in the group receiving irradiation. Proportions of females and CSIIE patients were not significantly different between the two groups (\(P=1.0\) for females; \(P=0.33\) for CSIIE by Fisher’s exact test). All rituximab-treated patients (\(n=10\)) achieved and maintained complete remission during the clinical follow-up (6–29 months). There were no critical adverse events associated with the monthly infusion of rituximab. As all patients achieved complete remission and were alive during the follow-up period, EFS, defined as survival without evidence of disease progression or relapse, was calculated by Kaplan–Meier methods according to the treatment modalities.

EFS with the monthly administration of rituximab was sustained for a prolonged period (Figure 1). Two of eight patients relapsed in 24–26 months after the completion of radiotherapy. All patients treated with irradiation complained of dacryoadenitis, conjunctivitis, visual acuity loss or cataract. EFS of the patients receiving irradiation and monthly rituximab monotherapy is shown in Figure 1. These results demonstrated that EFS rates with the monthly administration of rituximab and that of radiotherapy were comparable (\(P\)-value = 0.37).

The recent availability of rituximab has improved the EFS, progression-free survival (PFS) and overall survival of patients with B-cell non-Hodgkin’s lymphoma. The frequency and severity of its

Table 1. Characteristics of patients diagnosed with OAL

| Pt. no. | Age (years) | Gender | CS | Rituximab (cycles) | RT (Gy) | Outcome | Relapse | Complications (> grade 2) |
|---------|-------------|--------|----|--------------------|---------|---------|---------|--------------------------|
| 1       | 36          | M      | IE | 8                  | NA      | CR      | ND      | ND                       |
| 2       | 70          | F      | IE | 8                  | NA      | CR      | ND      | ND                       |
| 3       | 47          | F      | IIE| 8                  | NA      | CR      | ND      | ND                       |
| 4       | 79          | M      | IE | 8                  | NA      | CR      | ND      | ND                       |
| 5       | 76          | M      | IE | 8                  | NA      | CR      | ND      | ND                       |
| 6       | 74          | M      | IIE| 8                  | NA      | CR      | ND      | ND                       |
| 7       | 71          | M      | IE | 8                  | NA      | CR      | ND      | ND                       |
| 8       | 46          | F      | IE | 8                  | NA      | CR      | ND      | ND                       |
| 9       | 65          | F      | IE | 8                  | NA      | CR      | ND      | ND                       |
| 10      | 64          | M      | IIE| NA                 | 30.6    | CR      | ND      | Conjunctivitis           |
| 11      | 43          | F      | IIE| NA                 | 30.0    | CR      | ND      | Cataract                 |
| 12      | 81          | M      | IIE| NA                 | 30.0    | CR      | ND      | Conjunctivitis           |
| 13      | 82          | F      | IIE| NA                 | 30.0    | CR      | ND      | Cataract, conjunctivitis |
| 14      | 77          | M      | IIE| NA                 | 30.6    | CR      | ND      | Cataract, decreased visual acuity |
| 15      | 67          | M      | IE | NA                 | 30.6    | CR      | ND      | Cataract                 |
| 16      | 81          | F      | IIE| NA                 | 45.0    | CR      | Locally relapsed         | Dacryoadenitis           |
| 17      | 69          | M      | IE | 8                  | 30.0    | CR      | Locally relapsed         | Conjunctivitis, visual acuity |

Abbreviations: CR, complete remission; CS, clinical stage; NA, not applicable; ND, not determined; RT, dose of radiotherapy. Patient no. 17 received eight cycles of rituximab following relapse after achieving CR by RT.
side effects are non-significant during mono-treatment. Thus, rituximab is currently one of the prerequisite drugs for patients with B-cell non-Hodgkin’s lymphoma, especially for the aged. It was reported that four weekly cycles of rituximab at doses of 375 mg/m² as induction therapy were significantly effective in patients with OAL, but early recurrence was common.2,11,12 Ardeshana et al.13 reported that four weekly rituximab doses of 375 mg/m² followed by maintenance therapy every couple of months for 2 years improved PFS compared with induction therapy alone for advanced and asymptomatic follicular lymphoma, which belongs to indolent lymphoma, in which mucosa-associated lymphoid tissue-type lymphoma is classified. Notably, it is of interest that the 2-year PFS in the rituximab induction group was equivalent to the 4-year PFS in the maintenance group, and furthermore, the 4-year PFS in the former was almost the same as the 6-year PFS in the latter,13 suggesting that the duration of exposure to even a low concentration of rituximab is more critical than its concentration.

The alternative modality of radiotherapy is a promising tool for OAL. As OAL is not a systemic disease, the treatment should preserve the quality-of-life of patients with less adverse effects, such as long-term toxicity causing cataract (30–50%), xerophthalmia (20–40%), ischemic retinopathy, optic atrophy, corneal ulceration and neovascular glaucoma, as well as immediate toxicity including conjunctivitis, conjunctival ulcer and dry eyes.2,6–10,14,15 Patients with OAL receiving local irradiation also suffer from dry eye, cataract and conjunctivitis based on our experience. As OAL is associated with quite a favorable prognosis, therapeutic options that preserve the quality-of-life of patients with less adverse effects are chosen. Thus, we decided on the monthly administration of rituximab and radiotherapy for patients receiving irradiation and rituximab therapy is shown. Dotted and solid lines indicate EFS in patients with radiotherapy or rituximab alone, respectively.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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