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Rituximab induction therapy, survival benefits, and the increasing selection of radiotherapy as post-induction treatment in patients with primary mediastinal large B cell lymphoma

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ABSTRACT

Background: Primary mediastinal large B-cell lymphoma (PMBCL) is a rare malignancy that has been reported in younger individuals, especially young women. Patients with PMBCL commonly receive rituximab induction. This single-institution study was designed to analyze rituximab induction's clinical benefits and impact on the usage of post-induction treatments (PIT), especially radiotherapy.

Methods: The benefits of rituximab induction were evaluated in terms of complete response (CR), early treatment failure, relapse, and overall survival (OS) rates. The induction therapy's impact on the adoption of PIT was evaluated in terms of the proportions of patients who had received any PIT modality (either radiotherapy or hematopoietic stem cell transplantation [HSCT]), radiotherapy alone, HSCT alone, or both modalities at the last follow-up.

Results: Between 1999 and 2012, 48 PMBCL patients (29 men, 60%) were identified, with a median age of 31 years. Twenty-eight patients received rituximab induction, of whom 23 (82% of 28) also underwent fludeoxyglucose-positron emission tomography (FDG-PET) evaluation. Rituximab induction was significantly associated with higher rates of CR and OS, as well as lower rates of early treatment failure and relapse. Regarding PIT, patients with rituximab induction tended to be more likely to receive radiotherapy alone (with vs. without rituximab induction: 5% vs. 25%), as did patients with FDG-PET evaluation (with vs. without FDG-PET evaluation: 0% vs. 28.6%). Upon multivariate analysis, age >60 years (hazard ratio [HR], 16.697; 95% confidence interval [CI], 1.106–252.022; *P*=0.042) and rituximab induction (HR, 0.089; 95% CI, 0.012–0.653; *P*=0.017) were significantly associated with OS.

Conclusion: In conclusion, rituximab improved both the CR and OS rates of patients with PMBCL, but these improvements might be attributable to the increased use of radiotherapy (which may have resulted from FDG-PET evaluation as well).

Keywords: overall survival, positron emission tomography, primary mediastinal large B-cell lymphoma, radiotherapy, rituximab

INTRODUCTION

Primary mediastinal large B-cell lymphoma (PMBCL) is a relatively rare malignancy, accounting for only 2% of all cases of non-Hodgkin's lymphoma (NHL).[1] As compared with patients who have diffuse large B cell lymphoma, not otherwise specified (DLBCL, NOS; abbreviated as DLBCL hereafter), patients with PMBCL are reported to be younger at diagnosis and predominantly female.[1] Regarding chemotherapy induction therapy, several large-scale analyzes performed in Western countries have shown that the third-generation chemotherapy regimen MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) is associated with a higher response rate;[2] however, CHOP-21 (cyclophosphamide, doxorubicin or epirubicin, vincristine, and prednisone every 21 days) is commonly used in Asian countries.[3-6] In addition, the disease might be controlled further by post-induction treatments (PIT), such as radiotherapy[7] and/or high-dose therapy plus autologous hematopoietic stem cell transplantation (HSCT).[8,9]

Since the 2000s, rituximab and fludeoxyglucose-positron emission tomography (FDG-PET) have been commonly used in the management of B-cell NHL, including PMBCL. Several recent reports have demonstrated that the addition of rituximab in induction therapy (hereafter referred to as rituximab induction) is associated with improved rates of response and progression-free survival.[10,11] FDG-PET is usually employed to decide whether these patients should receive additional radiotherapy, especially for those patients who have suspicious residual or recurrent lesions in the mediastinum.[12,13] However, in their phase II trial of the combination of dose-adjusted EPOCH (etoposide, prednisone, oncovin [vincristine], cyclophosphamide, and hydroxyldaunorubicin [doxorubicin]) and rituximab (DA-EPOCH-R), Dunleavy *et al*. demonstrated that end-of-treatment FDG-PET evaluation of PMBCL patients had a relatively low positive predictive rate (17%), based on the pathological findings of PET-positive lesions.[14] In the non-trial setting, the rate of biopsy for this malignancy is low, and it is therefore anticipated that the use of

radiotherapy will increase for PMBCL, especially following rituximab-containing immunochemotherapy. In the current study, we capitalized upon our experience with cases of PMBCL to perform a single-institution investigation of rituximab's clinical benefits, evaluated in terms of treatment response, relapse, and survival. Further, we sought to illustrate the evolution of PIT following the adoption of rituximab induction.

METHODS

Patients

We reviewed the records of patients who had B-cell NHL and had been admitted to our hospital between 1999 and 2012. All patients with (1) the mediastinum as the primary site of neoplastic growth, as recognized on computed tomography (CT), and (2) a pathological diagnosis of DLBCL for the mediastinal mass were identified and reclassified as having PMBCL according to the 2008 World Health Organization (WHO) classification.[1] After excluding two identified patients who did not receive treatment at our hospital, a total of 48 patients were enrolled in the present study. Information was collected regarding clinical features at diagnosis, treatments, and outcomes at the latest follow-up (as of November 2013). This retrospective study was approved by the Institutional Review Board of our hospital.

The clinical features that were analyzed included age, gender, performance status (according to the Eastern Cooperative Oncology Group [ECOG] scale), specific symptoms, serum lactate dehydrogenase (LDH) levels, involvement of extranodal sites (including the bone marrow), and clinical stage. In regard to specific symptoms at diagnosis, superior vena cava (SVC) syndrome was defined by imaging evidence of SVC encased by neoplastic growth plus the presence of clinical symptoms, including facial swelling, chest discomfort, or superficial vein engorgement over the anterior chest wall. Cases in which the greatest dimension of the mediastinal tumor measured >10 cm were defined as bulky disease. Disease stages were defined according to the Ann Arbor system,

and patients who had lesions that were limited to above the diaphragm with pleural effusion or pericardial effusion were defined as having stage IIE disease if no lymphoma cells were found in the effusion. In addition, International Prognostic Index (IPI) scores were calculated according to the published criteria.[15]

Treatments

Induction treatment consisted of chemotherapy with 6–8 cycles of the CHOP-21 regimen and, since 2005, CHOP-21 and rituximab (R-CHOP-21).

PIT was defined as radiotherapy and HSCT in the consolidation or salvage setting. Consolidation PIT was given (1) when the response to treatment was less than a complete response (CR) or an unconfirmed complete response (CRu) after induction and/or (2) if negative prognostic factors indicating an elevated risk of relapse (bulky disease or poor IPI) had been identified at diagnosis, as determined at the discretion of the physicians involved. Salvage PIT was usually administered for relapsed or refractory disease.

Radiotherapy was generally administered whenever any suspicious or definite residual lesion was found in the mediastinum after induction or salvage therapy. The mobilization of peripheral blood stem cells was done following chemotherapy with second-line regimens (e.g., ESHAP [etoposide, methylprednisolone, high-dose cytarabine, and cisplatin]). The main preparative regimens of HSCT were BEAC and BEAM (busulfan, etoposide, cytarabine, and cyclophosphamide or melphalan). Autologous HSCT was usually performed as consolidation or salvage therapy for patients with response to chemotherapy using second-line regimens, and allogeneic HSCT was only considered for those with refractory disease following chemotherapy using second-line regimens.

Response Evaluation

Treatment responses were evaluated using CT or FDG-PET after every 3–4 cycles of induction therapy and after 2–3 cycles of salvage chemotherapy; before and after radiotherapy and HSCT; and/or whenever there was clinical evidence indicating poor response or relapse. CR, CRu, partial response (PR), and progressive disease (PD) were defined according to previously reported criteria[16,17] and were adjusted according to whether FDG-PET had been used, which was determined at the discretion of the physicians involved.

End Points

The primary end point of the present study was the clinical benefit of rituximab induction, which was evaluated in terms of the differences between the response, early treatment failure (ETF), relapse, and overall survival (OS) rates of patients who had and had not received rituximab induction. Patients with PMBCL were classified as having ETF if they had experienced both a slow or inadequate response to 2–3 cycles of induction therapy (as determined according to the discretion of the physicians involved) and had received chemotherapy with second-line regimens earlier. Hence, the definition of ETF was modified from those previously described,[11] which included (1) early death during induction chemotherapy, (2) premature treatment withdrawal as a result of SD and switch to salvage therapy, and (3) PD or relapse within 6 months from treatment initiation or within 4 weeks from the end of chemotherapy (prior to or at postchemotherapy restaging). OS was measured from the time of diagnosis to the date of death from any cause or the time of the last follow-up.

The secondary end point of the study was the relevance of rituximab induction to the evolution of PIT in patients with PMBCL. The evolution of PIT was evaluated in terms of the proportions of patients who had received any PIT modality by the time of the last follow-up. PIT modalities were classified as either radiotherapy alone, HSCT alone, or the combination of both modalities. In addition, because rituximab and FDG-PET were applied at fairly similar times during

the clinical care of patients with PMBCL, we also examined the impact of FDG-PET on the evolution of PIT. We analyzed the associations of PIT with rituximab induction and FDG-PET evaluation separately, since patients receiving rituximab did not always undergo FDG-PET. It was assumed that the decision to administer PIT could only have depended on FDG-PET findings in those patients who received FDG-PET during both the treatment and follow-up periods. For concision, the term "FDG-PET evaluation" is employed in this manuscript to describe cases with FDG-PET evaluations during both treatment and follow-up.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows v. 17.0 (SPSS Inc., Chicago, IL). Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, whereas continuous variables were compared using the t-test or the Mann-Whitney rank-sum test. The Kaplan-Meier method was used to estimate OS, and the log-rank test was used to compare the survival of patients with different prognostic factors and treatments. Multivariate Cox proportional hazards regression analysis was used to identify factors that were independently associated with OS (with 95% confidence intervals [CIs]) after adjusting for the factors that had *P* values less than 0.1 in univariate analyses. For all analyses, *P* values less than 0.05 were considered statistically significant.

RESULTS

Clinical Characteristics at Diagnosis According to Rituximab Induction Therapy

A total of 48 patients were included in our analysis (29 males [60%]; median age, 31 years; range, 16–85 years; Table I). Eight patients (17%) were older than 60 years. At diagnosis, symptoms of SVC syndrome and a bulky mass were found in 21/47 (45%) and 27/45 (60%) patients, respectively.

Thirty-eight of 45 patients (84%) had elevated serum LDH levels. Thirteen (27%) patients had advanced stages (III or IV) of disease, 25/45 (55%) patients had an intermediate-to-high IPI score (≥2) at diagnosis, and 28 (58%) patients received rituximab induction. Patients with and without rituximab induction had similar demographics (Table I).

PIT and Outcomes According to Rituximab Induction Therapy

As compared with their counterparts, patients with rituximab induction were more likely to have undergone FDG-PET for response evaluations (82% vs. 25%, $P<0.001$; Table II). In addition, rituximab induction was associated with significantly higher CR/CRu (86% vs. 50%, $P=0.024$) and lower ETF (11% vs. 65%, $P<0.001$) rates. The lower ETF rate in patients with rituximab induction reflected the combination of differences in early death rates (with vs. without rituximab induction: 4% vs. 15%), premature treatment withdrawal rates (0% vs. 20%), and early PD or relapse rates (7% vs. 30%).

In regard to PIT modalities (Table II), the proportion of cases that included radiotherapy was similar in patients with and without rituximab induction (43% vs. 45%, respectively), whereas patients with rituximab induction were more likely to have received radiotherapy as a consolidation therapy because CT or FDG-PET revealed residual lesions in the mediastinum (39% vs. 5%, $P<0.001$). In addition, patients with rituximab were less likely to have received HSCT (43% vs. 70%, $P=0.014$), and HSCT was used as a consolidation therapy in a higher proportion of their cases. Of the 25 patients who received HSCT once, seven (28%) received allogeneic HSCT as salvage therapy, including three patients who received autologous HSCT.

Distribution of PIT According to Classification of Rituximab Induction or FDG-PET Evaluation

Because many patients who received rituximab induction also underwent FDG-PET for evaluations of PMBCL, we further investigated the use of PIT according to both rituximab induction and

FDG-PET evaluation status. As shown in Table III, we found that FDG-PET evaluation was significantly associated with the distribution of PIT (P=0.03). In comparison with patients who did not undergo FDG-PET evaluation, a higher proportion of the patients who underwent FDG-PET evaluation received radiotherapy alone, while a lower proportion received both radiotherapy and HSCT. A similar trend was observed for rituximab induction (Table III).

Survival and Prognostic Factors

The median duration of follow-up was 67.2 months (range, 7.1–150 months). At last follow-up, 36 patients (75%) were alive and disease free. The 3-year OS rate was 73%. Patients with rituximab induction had a better mean duration of OS than those without rituximab induction (90.9 months vs. 88.5 months, P=0.011; Table II and Figure 1). The causes of death included uncontrolled lymphoma in three patients, and treatment-related neutropenia and infection in nine patients (Table II).

As shown in Table IV, we evaluated the univariate relationships between several factors and OS. Factors that were associated with poor OS included age older than 60 years, the presence of SVC syndrome, higher IPI risk groups at diagnosis, the absence of rituximab induction, and the absence of any PIT. When all factors with P values < 0.1 (except for the IPI risk group) were included in the multivariate Cox regression analysis, age older than 60 years (hazard ratio [HR], 16.697; 95% CI, 1.106–252.022; P=0.042) and rituximab induction (HR, 0.089; 95% CI, 0.012–0.653; P=0.017) were found to be independent prognostic factors for OS. Further, SVC syndrome at diagnosis tended to be associated with poor OS.

DISCUSSION

Based on clinical experiences at a single institution, this study's findings not only demonstrate the clinical benefits of rituximab induction in cases of PMBCL, but also illustrate the associations

between rituximab induction and PIT; particularly, rituximab induction was associated with increased use of radiotherapy alone. When administered to patients with PMBCL, rituximab induction resulted in improved CR/CRu and OS rates, as well as reduced ETF and relapse rates. These findings are similar to the results of several recent studies.[5,10,11,18] Moreover, rituximab induction was found to be associated with greater use of radiotherapy as consolidation therapy, rather than as salvage therapy (Table III), although the proportion of PMBCL patients who finally received radiotherapy was similar with or without rituximab induction (45% vs. 43%, Table II). In fact, the proportion of our patients who received radiotherapy might have been reduced because of the early adoption of front-line HSCT. Several recent studies have demonstrated trends of increased radiotherapy use in PMBCL patients who received rituximab induction. Among German patients with PMBCL, radiotherapy was slightly more common in cases with rituximab (73%) than in cases without rituximab (67%).[10] Similarly, the proportion of Greek patients undergoing radiotherapy was greater among cases with rituximab (70%) than among cases without rituximab (48%),[11] and the proportion undergoing radiotherapy further increased to 89% in a report by the International Extranodal Lymphoma Study Group (IELSG).[19]

Our present results, as well as the above-mentioned studies, showed that most patients with PMBCL (1) experienced a good treatment response following induction therapy with R-CHOP-21 and (2) began to receive radiotherapy because of CT or FDG-PET scans that showed an avid residual lesion in the mediastinum. These findings have both positive and negative implications. First, R-CHOP-21 alone remains insufficient as a means of fully controlling PMBCL.[20] It is possible that FDG-PET improves the detection of small residual lesions in the mediastinum, which could explain the greater administration of radiotherapy in the patients with PMBCL who underwent FDG-PET. However, radiotherapy might be not necessary in some cases of PMBCL, as shown by Dunleavy *et al.*'s study of DA-EPOCH-R.[14] Furthermore, radiotherapy was not shown to confer a benefit in terms of the OS of PMBCL patients with or without rituximab, either in our own

study or in several previous studies.[10,11]

Rituximab induction and subsequent FDG-PET evaluation have probably contributed to the increased use of radiotherapy in patients with PMBCL. Our attempts to weigh the individual influences of rituximab induction and FDG-PET evaluation were limited by their fairly similar application times and the relatively small number of patients in this study. Nonetheless, the findings of several recent studies have supported this theory. Han *et al*. and Avivi *et al*. reported that rituximab induction in DLBCL patients was associated with higher false positive rates of FDG-PET, as compared with the false positive rates of FDG-PET in DLBCL patients without rituximab induction, possibly as a consequence of immune-mediated inflammation.[21,22] Pregno *et al*. and Avigdor *et al*. showed that interim FDG-PET failed to predict the outcomes of DLBCL patients treated with R-CHOP[23] and the outcomes of PMBCL patients following R-VACOP-B and R-CHOP-21,[24] respectively. Most importantly, by aggressively performing biopsies, Dunleavy *et al*. clearly demonstrated that end-of-treatment FDG-PET had a relatively high false positive rate following DA-EPOCH-R therapy.[14] Because PMBCL patients are usually relatively young, radiotherapy of the mediastinum is potentially associated with long-term sequelae, as are seen in patients with Hodgkin disease.[25,26] Recently, the Deauville 5-point criteria has increasingly been used to interpret FDG-PET-positive residual lesions in the mediastinum after rituximab induction.[27] This approach will provide a basis for using PET/CT to define the role of radiotherapy in PMBCL.[19]

Another interesting finding of our study was the predominance of male patients in our study cohort. This finding contrasts with most studies from Western countries,[12,28] whereas several reports from China,[29] Japan,[3] Canada,[30] as well as from other hospitals in Taiwan[31,32] showed findings that are similar to our own (Table V).

This retrospective study is subject to several limitations. Although our institution is a veterans' hospital, this was not considered to be a confounding factor in our study since the median

age of our PMBCL patients was relatively low. It is possible that we enrolled patients with the disease known as mediastinal gray-zone lymphoma. Mediastinal gray-zone lymphoma usually presents with pathological features of both DLBCL and Hodgkin's disease,[33] and predominantly occurs among men.[34] Additional staining for PMBCL-specific transcription factors (e.g., cREL, MAL, and FIG-1[1]) might be used to resolve any accidental inclusion of mediastinal gray-zone lymphoma. However, such staining was not performed in the present study because of the limited number of available specimens. Since the IELSG study has suggested that male gender is an independent poor prognostic factor for patients with PMBCL,[12] geographic or racial differences in the gender distribution of PMBCL may be informative and warrant additional molecular studies to clarify the underlying pathogenesis. Furthermore, as compared with other reports,[10,11,19] the present study included a higher proportion of patients who received front-line HSCT, as well as a lower proportion of patients who received radiotherapy. Thus, it is possible that selected patients' benefits from front-line HSCT with CHOP-21 as induction chemotherapy may resemble the benefits of induction therapy with higher-intensity chemotherapy, such as MACOP-B[2] and DA-EPOCH.[14] Our investigation's ability to clearly demonstrate the benefits of radiotherapy and HSCT might have been limited by the heterogeneity of PIT in our patient cohort, as well as the relatively small number of patients. However, in the subset of our patients who did not receive rituximab induction, the CR/CRu rate was relatively low, suggesting that the prognosis of PMBCL patients was indeed improved by radiotherapy and/or HSCT as consolidation or salvage therapy. In our study, one patient was chemo-resistant to salvage chemotherapy and received radiotherapy and subsequent allogeneic HSCT; this patient remained disease-free at the latest follow-up (5 years post-transplant), which is similar to the findings of one previously reported study.[35]

In conclusion, the findings of our study demonstrate the clinical benefits of rituximab induction in patients with PMBCL who are treated with CHOP-21, the conventional chemotherapy regimen. In addition, our findings illustrate the changes to PIT that accompany rituximab induction,

which are characterized by an increased use of radiotherapy. However, these changes may be partially attributable to the use of FDG-PET evaluation. Considering the potential for long-term sequelae, treating physicians should carefully evaluate FDG-PET scan-positive lesions in PMBCL patients whenever radiotherapy is planned following rituximab induction.

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FIGURE LEGEND

Figure 1. Overall survival of patients with primary mediastinal large B cell lymphoma according to the use of rituximab induction