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HIV positivity may not have a negative impact on survival in Epstein-Barr virus-positive Hodgkin lymphoma: A Japanese nationwide retrospective survey

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Abstract. There has been no comparative clinical study focused on differences in the clinical features of Epstein-Barr virus (EBV)$^+$ Hodgkin lymphoma (HL) between HIV-positive and -negative cases. In a nationwide survey from 511 institutions in Japan, the present study investigated 16 EBV+ HIV^{positive} HL patients. To further clarify their characteristics in comparison with EBV+ HIV^{negative} HL (n=34) in the combination antiretroviral therapy era in Japan, the present study was performed. Results indicated that EBV$^+$ HIV^{positive} HL frequently occurred in a younger population compared with EBV$^+$ HIV^{negative} HL (P=0.0295), and that the EBV$^+$ HIV^{positive} HL group was not associated with the nodular sclerosis subtype in the population who were below the age of 40. Notably, the EBV$^+$ HIV^{positive} HL group had a significantly higher frequency of extra-nodal involvement (P=0.0214), including marrow invasion. In the advanced stage, 80% of those with EBV$^+$ HIV^{positive} HL did not require dose-reduction and in the majority of cases, chemotherapy was completed. There were no significant differences in the complete remission rate (P=0.1961), overall survival (P=0.200) and progression-free survival (P=0.245) between EBV$^+$ HIV^{positive} HL (median observational period, 23.5 months) and EBV$^+$ HIV^{negative} HL (median observational period, 64.5 months), suggesting that HIV positivity may not have a negative impact on the clinical outcome of EBV$^+$ HL. Notably, standard chemotherapy is effective and tolerable for EBV$^+$ HL, regardless of HIV infection.

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Introduction

The incidence of Hodgkin lymphoma (HL) in human immunodeficiency virus (HIV)-infected individuals has been increasing across countries since the advent of combination antiretroviral therapy (cART), and HL is presently one of the most frequent non-AIDS defining malignancies (1-3). Therefore, HIV^{positive} HL is currently an important complication of HIV infection in the cART era.

Our previous nationwide survey in Japan demonstrated that most HIV^{positive} HL patients are EBV-positive (EBV$^+$) (4). Epstein-Barr virus (EBV) is considered to play a role in the pathogenesis of an HL subset (5,6); however, the frequency of EBV association in HL is markedly different between HIV^{positive} HL (80-100%) and HIV^{negative} HL (20-50%) (5-8). In HIV negative cases, EBV positivity is demonstrated to have a male predominance, a high incidence of mixed cellularity classical Hodgkin lymphoma (MCCHL), and advanced clinical stages (9). The prognostic impact of EBV positivity in HL remains controversial (9-12). It has been recently reported that HIV infection has no prognostic impact on advanced-stage HL (13). However, to the best of our knowledge, there has been no comparative clinical study that focused on the differences in the clinical features of EBV$^+$ HL between HIV positive

and negative cases. Thus, we planned an expanded survey to compare the clinical characteristics between HIV^{positive} HL and HIV^{negative} HL with pathologically detectable EBV in a Japanese population.

Patients and methods

In our previous retrospective nationwide study in Japan between 1991 and 2010 from 511 institutions among all regional centers and all educational hospitals certified by the Japanese Society of Hematology (4,14), there were only 19 HIV^{positive} HL patients. Among them, we found 16 evaluable EBV^{+} HIV^{positive} HL patients for analysis in this study. The criteria for EBV-positivity were defined by EBER *in situ* hybridization and/or LMP-1 immunostaining (4). In addition, data of newly obtained 123 HIV^{negative} HL patients who visited three regional hospitals (i.e., Cancer Institute Hospital of JFCR, National Hospital Organization Nagoya Medical Center, and Tokyo Medical University) between 2001 and 2010 were used for this study. Chart reviews were performed for all identified patients (Table I). We further re-assessed the pathological diagnosis and performed additional immunostaining for EBV assessment, as defined by EBER *in situ* hybridization and/or LMP-1 immunostaining, and finally identified 34 HIV^{negative} EBV^{+} HL patients as a control. This study was approved by the Ethics Committee of Tokyo Medical University Hospital (no. 2610; February 4, 2014), Cancer Institute Hospital of JFCR, and National Hospital Organization Nagoya Medical Center.

Response was assessed according to the International Workshop Criteria for non-Hodgkin's lymphoma (15). Overall survival (OS) was defined as the interval from HL diagnosis to death from any cause. Progression-free survival (PFS) was defined as the interval from HL diagnosis and the date on which disease progresses or the date on which the patient dies from any causes. Two HIV^{positive} HL patients diagnosed by autopsy were excluded from prognostic analysis. International Prognostic Score (IPS) was evaluated according to a previous report (16). Treatment completion was defined as completing the induction therapy without discontinuance. Dose reduction was defined as a 10% or more reduction in the optimal dose calculated according to body surface area. One HIV^{positive} HL patient was being treated with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) at the time of this study and was therefore excluded from the analysis of treatment completion and dose reduction. Two HIV^{negative} HL patients without evaluable clinical response were excluded from the analysis of the response rate and treatment completion (Table I).

Statistical analysis. Age difference according to HIV status was assessed using the Wilcoxon signed rank test. The difference in clinical parameters according to the HIV status was assessed using the chi-square test or Fisher's exact test, when appropriate. Overall survival and PFS between groups divided by the HIV status were compared using the log-rank (Mantel-Cox) test. GraphPad Prism software (version 5c for Macintosh; GraphPad Software Inc., La Jolla, CA, USA) was used for the statistical analysis, and P-values <0.05 were considered to indicate a statistically significant difference.

Results

Details of EBV-positivity. Among 19 HIV^{positive} HL patients in the previous study, there were 16 EBV-positive patients (EBER and/or LMP-1 positive 16, negative 2, unknown 1). Among the newly obtained 123 HIV^{negative} HL patients, there were 34 EBV-positive patients (EBER and/or LMP-1 positive 34, negative 43, unknown 5, not operated 42).

Characteristics of EBV^{+} HIV^{positive} Hodgkin lymphoma patients. The clinicopathologic features of 50 EBV^{+} HL patients, consisting of 16 HIV^{positive} and 34 HIV^{negative} patients, are summarized in Table I. All HIV^{positive} patients, but one, had HL diagnosis in the cART era (i.e., after 1997); 14 of the 16 HIV^{positive} patients developed HL during the HIV follow-up at 40 (median) months (range, 6-84) after HIV diagnosis, and the remaining two were initially found to have HIV infection at the time of HL diagnosis. The HIV^{positive} HL patients were significantly younger in terms of median age than the HIV^{negative} HL patients (45 years old vs. 60.5 years old: P=0.0158). The median CD4^{+} cell count (CD4^{+} count) at HL diagnosis was 231/μl (range, 1-567/μl) in HIV-positive cases.

The most common subtype of HL was MCCHL in the EBV^{+} HIV^{positive} group and EBV^{+} HIV^{negative} group (68.8% vs. 61.8%, respectively). The patient's peak age of MCCHL incidence in the EBV^{+} HIV^{positive} group was in their 30s, whereas that in the EBV^{+} HIV^{negative} group was in their 60s (Fig. 1A and B). Patients in their 20s were not observed in the HIV^{positive} group; patients in the EBV^{+} HIV^{negative} group showed a peak incidence of nodular sclerosis classical Hodgkin lymphoma (NSCHL) in their 20s and of MCCHL in their 60s similarly to previous reports (17,18) (Fig. 1A). By contrast, no case of NSCHL was encountered in the EBV^{+} HIV^{positive} group particularly in the patients who were below their 40s (Fig. 1B).

There were no significant differences in the incidence of advanced stage between the HIV^{positive} group and the HIV^{negative} group (81.3% vs. 67.6%: P=0.258), or in the presence of B symptom (50% vs. 41.2%: P=0.388). In contrast, significantly higher incidences of extranodal involvement (56.3% vs. 20.6%: P=0.0150) and BM involvement by itself (47.8% vs. 2.9%: P=0.000748) were observed in the EBV^{+} HIV^{positive} group (Table I).

Treatment response and survival. The complete remission (CR) rate of the HIV^{positive} HL patients was not significantly different from that of the HIV^{negative} HL patients (84.6% vs. 96.9%: P=0.196) (Table I). The OS of the EBV^{+} HIV^{positive} HL patients, including one patient under treatment, (median observational period, 23.5 months) was not significantly different from that of the EBV^{+} HIV^{negative} HL patients (median observational period, 64.5 months) (5-year OS probability: 65.1% vs. 79.0%; P=0.1921) (Fig. 2A). There was no significant difference in the PFS between EBV^{+} HIV^{positive} HL and EBV^{+} HIV^{negative} HL (5-year PFS probability: 66.8% vs. 78.7%; P=0.2835) (Fig. 2B).

The treatment completion rate of the advanced-stage patients treated with ABVD/ABVd was 90.0% in the HIV^{positive} HL patients and 75.0% in the HIV^{negative} HL patients (P=0.326) (Table I). The rate of the patients with ABVD/ABVd dose

Table I. Baseline characteristics of EBV+ HL patients with and without HIV.

Variable	EBV^{+} $HIV^{positive}$ HL (n=16)	EBV^{+} $HIV^{negative}$ HL (n=34)	P-value
Male/female	14/2	25/9	0.232[A]
Median age, years (range)	45 (31-66)	60.5 (20-85)	**0.0158[B]**
Absolute $CD4^{+}$ cell count, cells x 10^{9}/l (range)	231 (1-567)	ND	
Viral load <500 copies/ml	10/14[a]	ND	
On ART	13/16 (81.3%)	0/34	
Histological subtype n (%)			
NSCHL	3 (18.8%)	8 (23.5%)	
MCCHL	11 (68.8%)[b]	21 (61.8%)	0.631[C]
LRCHL	0 (0%)	5 (14.7%)	
LDCHL	1 (6.3%)[c]	0 (0%)	
Non-specific	1 (6.3%)	0 (0%)	
Ann Arbor stage n (%)			
Localized stage	3 (18.8%)	11 (32.4%)	0.258[A]
Advanced stage	13 (81.3%)[d]	23 (67.6%)	
Symptoms in category B of Ann Arbor staging[D]	8 (50.0%)[e]	14 (41.2%)	0.388[A]
Extranodal lesion	9 (56.3%)[f]	7 (20.6%)	**0.015[A]**
Bone marrow involvement	7/16 (47.8%)[g]	1 (2.9%)	**0.000748[A]**
IPS			
0-2	7 (43.8%)	16 (47.1%)	0.498[A]
≥3	9 (56.3%)[h]	17 (50.0%)	
Unknown		1 (2.9%)	
Treatment			
Localized stage			
ABVD	0	4	
RT	1	1	
ABVD+RT	2	6	
Advanced stage			
ABVD/ABVd	11	20	
ABVD+RT	0	1	
C-MOPP	0	1	
BD[i]	0	1	
No treatment[j]	2	0	
Complete remission rate	11/13 (84.6%)[k]	31/32 (96.9%)	0.196[A]
Treatment completion rate (advanced stage)	9/10 (90%)[l]	15/20 (75.0%)	0.326[A]
Rate of patients with ABVD/ABVd dose reduction	2/10[m]	0/20	0.103[A]
Auto PBSCT	0	1	

P<0.05 is indicated in bold. [a]Two $HIV^{positive}$ HL patients were excluded because of missing data. [b]including one $HIV^{positive}$ HL patient diagnosed by autopsy. [c]including one $HIV^{positive}$ HL patient diagnosed by autopsy. [d]Two $HIV^{positive}$ HL patients diagnosed by autopsy were in the advanced stage. [e]Two $HIV^{positive}$ HL patients diagnosed by autopsy had symptoms. [f]Two $HIV^{positive}$ HL patients diagnosed by autopsy had extranodal lesion. [g]Two $HIV^{positive}$ HL patients diagnosed by autopsy had bone marrow involvement. [h]Two $HIV^{positive}$ HL patients diagnosed by autopsy were IPS≥3. [i]The patient received only bleomycin and dacarbazine according to patient's request. [j]Two $HIV^{positive}$ HL patients diagnosed by autopsy received no treatment. [k]Two $HIV^{positive}$ HL patients diagnosed by autopsy and one $HIV^{positive}$ HL patient on treatment were excluded from the analysis of complete remission rate. [l,m]Among 13 advanced stage $HIV^{positive}$ HL patients, two patients diagnosed by autopsy and one patient on treatment were excluded from the analysis of response rate, treatment completion, and rate of patients with ABVD/ABVd dose reduction. . [A]Fisher's exact test; [B]Wilcoxon signed rank test; [C]Chi-square test; [D]fever, night sweats and body weight loss. ART, antiretroviral therapy; NSCHL, nodular sclerosis classical Hodgkin lymphoma; MCCHL, mixed cellularity classical Hodgkin lymphoma; LRCHL, lymphocyte-rich classical Hodgkin lymphoma; LDCHL, lymphocyte-depleted classical Hodgkin lymphoma; IPS, International Prognostic Score; ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; RT, radiotherapy; ABVd, ABVD therapy with a lower dose of dacarbazine (250 mg/m^{2}); C-MOPP, cyclophosphamide, vincristine, procarbazine, prednisone; auto PBSCT, autologous peripheral blood stem cell transplantation.

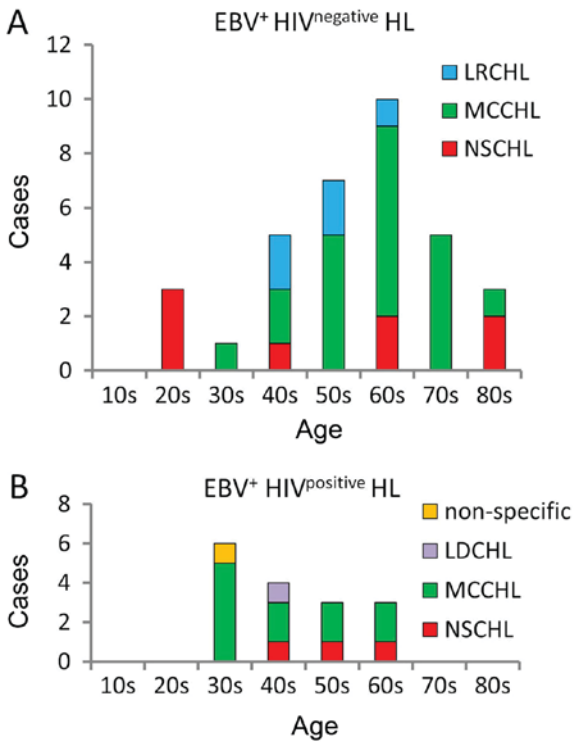

Figure 1. (A) Frequency of the pathological subtype of EBV+ HIV^{negative} Hodgkin lymphoma (HL) according to age. The peaks of HL incidence were observed in the patients who were in their 20s (NSCHL) and 60s (MCCHL) in the EBV+ HIV^{negative} HL patients. (B) Frequency of the pathological subtype of EBV+ HIV^{positive} HL according to age. There was no case of NSCHL in the patients who were in their 20s, and the peak incidence of MCCHL was observed in the patients who were in their 30s in the EBV+ HIV^{positive} HL patients. LDCHL, lymphocyte-depleted classical Hodgkin lymphoma; LRCHL, lymphocyte-rich classical Hodgkin lymphoma; MCCHL, mixed cellularity classical Hodgkin lymphoma; NSCHL, nodular sclerosis classical Hodgkin lymphoma.

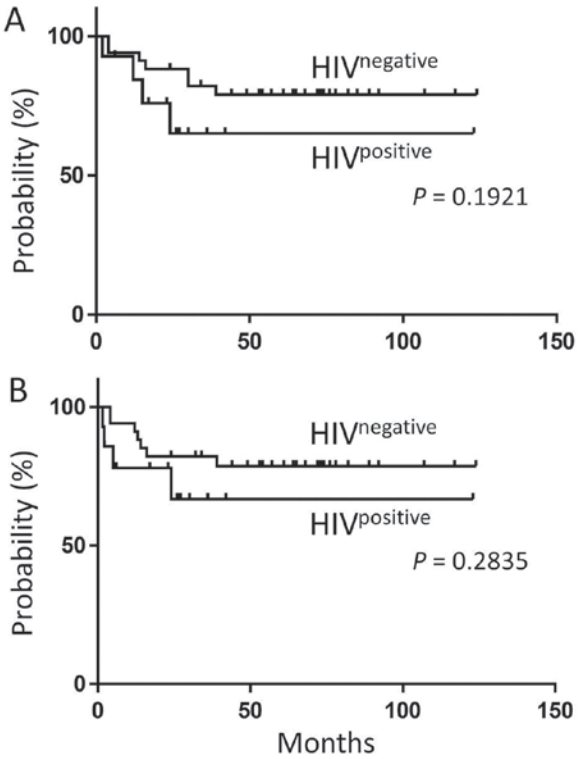

Figure 2. (A) Overall survival of EBV+ HIV^{positive} and HIV^{negative} HL patients. The OS probability of the EBV+ HIV^{positive} HL patients (n=14) was comparable to that of the EBV+ HIV^{negative} HL patients (n=34) (P=0.1921, log-rank test). Two HIV^{positive} HL patients diagnosed by autopsy were excluded from the prognostic analysis. (B) Progression-free survival (PFS) of EBV+ HIV^{positive} and EBV+ HIV^{negative} HL patients. The PFS of the EBV+ HIV^{positive} HL patients (n=34) was comparable to that of the EBV+ HIV^{negative} HL patients (n=14) (P=0.2835, log-rank test). Two HIV^{positive} HL patients diagnosed by autopsy were excluded from the prognostic analysis.

reduction was 2/10 in the HIV^{positive} HL patients and 0/20 in the HIV^{negative} HL patients (P=0.103). Three of the 11 HIV^{positive} HL patients who received ABVD/ABVd in the advanced stage expired due to disease progression.

The CR rate of the advanced-stage HIV^{positive} HL patients treated with ABVD/ABVd was 80.0% (8/10), whereas that of the HIV^{negative} HL patients treated with ABVD/ABVd was 94.7% (18/19). Among the advanced-stage patients treated with ABVD/ABVd, the 5-year OS rate of the EBV+ HIV^{positive} HL patients was not significantly different from that of the EBV+ HIV^{negative} HL patients (56.6% vs. 75.0%; P=0.2063), as well as the 5-year PFS rate (57.3% vs. 73.7%; P=0.2636). Of the 30 EBV+ advanced-stage HL patients, no significant difference in OS was found in the low IPS group (0-2) (P=0.696) or high IPS (≥3) group (P=0.177) by the log-rank test (data not shown).

Discussion

EBV infection is associated with an increased risk of EBV-positive HL. EBV may play a role in the pathogenesis of EBV-positive HL (5,6), but this aspect has not yet been fully clarified. There have been comparisons between HL with EBV positive and negative patients. A recent report by Koh *et al* describes the impact of EBV-positivity on HL in Korea (12). There have also been comparisons between HIV positive HL and HIV negative HL. However, there have been no comparison data on EBV-positive HL between HIV positive and negative patients. To find out the difference, we matched the condition of EBV-positivity and made a comparison between the HIV positive and negative groups. As EBV-positive HL and EBV-negative HL act differently, it is essential to divide EBV-positive HL from EBV-negative HL to elucidate the facts about the impact of HIV infection.

The frequency of HL in HIV-infected individuals has increased two-folds in the cART era (19). It is known that HIV^{positive} HL patients have distinct clinicopathological features such as a high rate of EBV positivity, advanced-stage disease (20-22), and unfavorable histological subtypes, including MCCHL and lymphocyte-depleted classical HL (4). On the other hand, MCCHL is more likely to be EBV-positive across all age groups, particularly in young adults (23). In the current study, the peak age of the patients at EBV+ HIV^{positive} HL diagnosis was during their 30s; this age distribution was quite different from that observed in general HL showing biphasic peaks. Notably, we never found NSCHL in the patients who were below their 40s in the EBV+ HIV^{positive} HL group, whereas NSCHL was generally found in younger HL patients likely in the EBV+ HIV^{negative} HL group (Fig. 1A and B). This dissociation of pathological subtypes in the young generation in HL regarding HIV^{positive} HL, particularly for NSCHL, should be

confirmed in other ethnic cohorts as EBV-positive lymphoma is frequently encountered in Asia.

We included two patients diagnosed by autopsy, since the data of diagnosis and stage did not affect the clinical results, including outcome (Table I). They were excluded from prognostic analysis.

We found that EBV^{+} HIV^{positive} HL showed a high frequency of extranodal involvement compared with EBV^{+} HIV^{negative} HL, in accordance with previous studies (20-22). In particular, BM involvement was notable (47.8%) in HIV-positive patients. Ann Arbor staging (P=0.5012) or IPS (P=0.7489) was not significantly different whether the condition was HIV-positive or not, and the response to therapy was comparative.

We cannot simply conclude that the comparative clinical outcome between EBV^{+} HIV^{positive} HL and EBV^{+} HIV^{negative} HL in this survey is linked to the different aged populations with different pathological subtypes. Nevertheless, even with the high frequency of BM involvement in EBV^{+} HIV^{positive} HL, there were no significant differences in the CR rate, OS probability, and PFS compared with EBV^{+} HIV^{negative} HL. The current study demonstrated that the standard chemotherapy for EBV^{+} HIV^{negative} HL was acceptable for EBV^{+} HIV^{positive} HL in the cART era, and we obtained almost even results in response to chemotherapy as well as outcome between these two groups. These results further suggest that Ann Arbor staging or IPS might be helpful for planning therapeutic strategies for HL patients, including EBV^{+} HIV^{positive} HL patients.

Introduction of new agents such as brentuximab vedotin for CD30 blockade or nivolumab for programmed death (PD)-1 blockade (24) for relapsed HL patients, and their combination with hematopoietic stem cell transplantation for younger patients are currently major topics. PD-1 is a regulator of the survival of virus-specific CD8^{+} T cells in HIV infection (25), and it also plays a wide role in HIV pathogenesis (26). Thus, PD-1 has emerged as an attractive potential therapeutic target. The clinical effects of humanized monoclonal antibodies for PD-1, including nivolumab, for EBV^{+} HIV^{positive} HL are still unknown. Therefore, we should pay more attention to the outcome of EBV^{+} HIV^{positive} HL when treated with new agents. As most EBV^{+} HIV^{positive} HL patients are younger than 60 years, and more than 60% of them show MCCHL, the therapeutic strategy for such patients is an important issue to resolve.

The limitations of this study include the retrospective nature of the analysis among different institutions and terms. Although we performed a nationwide survey in Japan, the number of patients is still small because of the low incidence of HL in Japan [5% of malignant lymphoma (27)]. Nevertheless, there have been apparently no data available regarding EBV^{+} HL patients with comparison based on the HIV status.

In conclusion, we found that EBV^{+} HIV^{positive} HL preferentially occurred in a younger population with no NSCHL, particularly in patients aged less than 40 years. In patients with the advanced stage of EBV^{+} HIV^{positive} HL, 80% of them did not require dose-reduction and most of them completed chemotherapy. Standard chemotherapy is effective and tolerable for EBV^{+} HL, regardless of HIV infection.

HIV positivity may not have a negative impact on the outcome in Japanese EBV^{+} HL. Thus, further evaluation of different ethnic cohorts is needed to provide additional information for delineating EBV^{+} HIV^{positive} HL in the cART era.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions

MY, YI, and KO analyzed and interpreted the patient data and were major contributors in writing the manuscript. SH contributed to the nationwide data collection of HIV-positive patients. YT and HN contributed for data collection of HIV-negative patients. YO contributed to the pathological examination. SO contributed to designing the study. AA, TU and JT contributed for offering data from their affiliations.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and local ethical legislation. This study was approved by the Ethics Committee of Tokyo Medical University Hospital (no. 2610; February 4, 2014), Cancer Institute Hospital of JFCR, and National Hospital Organization Nagoya Medical Center. Instead of obtaining informed consent from each patient, participants were given the opportunity to opt-out.

Consent for publication

Not applicable.

Competing interests

MY declare that they have no competing interests. NH received grants and personal fees from Chugai Pharmaceutical Co., grants and personal fees from Mundi Pharma, grants from Janssen Pharmaceutical K.K, Celgene Corporation, Bayer Yakuhin Ltd., Abbvie G.K., Takeda Pharmaceutical Co., Ltd., Bristol-Myers Squibb, and personal fees from Sanofi K.K and Esai Co., Ltd. outside the submitted work. KO received grants from Toyama Kagaku K.K., Nippon Shinyaku K.K., Pfizer, Bristol-Myers Squibb, Alexion Pharma K.K., Taiho Yakuhin, Asahikasei, Chugai Pharma K.K., and Jansen Pharma K.K, and personal fees from Celegen K.K., Novartis Pharma K.K., and Dainippon-Sumitomo Pharma outside the submitted work.

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