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ORIGINAL REPORT

VCAP-AMP-VECP Compared With Biweekly CHOP for Adult T-Cell Leukemia-Lymphoma: Japan Clinical Oncology Group Study JCOG9801

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ABSTRACT

Purpose
Our previous phase II trial for treating human T-lymphotropic virus type I–associated adult T-cell leukemia-lymphoma (ATLL) with vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP) showed promising results. To test the superiority of VCAP-AMP-VECP over biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), we conducted a randomized controlled trial exclusively for ATLL.

Patients and Methods
Previously untreated patients with aggressive ATLL were assigned to receive either six courses of VCAP-AMP-VECP every 4 weeks or eight courses of biweekly CHOP. Both treatments were supported with granulocyte colony-stimulating factor and intrathecal prophylaxis.

Results
A total of 118 patients were enrolled. The complete response (CR) rate was higher in the VCAP-AMP-VECP arm than in biweekly CHOP arm (40% *v* 25%, respectively; $P = .020$). Progression-free survival rate at 1 year was 28% in the VCAP-AMP-VECP arm compared with 16% in the CHOP arm ($P = .100$, two-sided $P = .200$). Overall survival (OS) at 3 years was 24% in the VCAP-AMP-VECP arm and 13% in the CHOP arm ($P = .085$, two-sided $P = .169$). For VCAP-AMP-VECP versus biweekly CHOP, grade 4 neutropenia, grade 4 thrombocytopenia, and grade 3 or 4 infection rates were 98% *v* 83%, 74% *v* 17%, and 32% *v* 15%, respectively. There were three toxic deaths in the VCAP-AMP-VECP arm.

Conclusion
The longer OS at 3 years and higher CR rate with VCAP-AMP-VECP compared with biweekly CHOP suggest that VCAP-AMP-VECP might be a more effective regimen at the expense of higher toxicities, providing the basis for future investigations in the treatment of ATLL.

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INTRODUCTION

Adult T-cell leukemia-lymphoma (ATLL) is a distinct peripheral T-lymphocytic malignancy associated with human T-cell lymphotropic virus type I.[1-3] The diverse clinical features of this disease have led to its classification.[4] Aggressive ATLL (ie, acute or lymphoma type) has usually been treated as a subtype of aggressive non-Hodgkin's lymphoma (NHL), whereas indolent ATLL (ie, chronic or smoldering type) has been managed as a subtype of chronic lymphoid leukemia.[5-7] Aggressive ATLL generally has a poor prognosis compared with aggressive B-cell lymphoma and peripheral T-cell lymphoma excluding ATLL.[7-9] Median survival time (MST) of patients with aggressive ATLL is approximately 8 months because of the multidrug resistance (MDR) phenotype of malignant cells, rapid proliferation of the cells, a large tumor burden with multiorgan failure, hypercalcemia, and/or frequent infectious complications.[4-7,10]

In the two previous multicenter trials for advanced NHL, Japan Clinical Oncology Group (JCOG) 8101 (1981 to 1983) and JCOG8701 (1987 to 1991) evaluating the efficacy of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) –like regimens and a multiagent regimen of the second generation, respectively, a significantly

shorter survival time was demonstrated for ATLL patients than for other NHL patients.[11,12] Thus, the first trial exclusively applied to aggressive ATLL, JCOG9109, was started (1991 to 1993). The chemotherapy protocol involved the use of deoxycoformycin, an inhibitor of adenosine deaminase, which was found to be effective against refractory ATLL.[13] However, there were no improvements in overall response rate (ORR) or survival time compared with the previous trials.[14]

The next phase II study (JCOG9303, 1994 to 1996), with the chemotherapy protocol LSG15 against aggressive ATLL consisting of a dose-intensified multiagent chemotherapy with vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP) with granulocyte colony-stimulating factor (G-CSF) and intrathecal prophylaxis, showed promising results with complete response (CR) and partial response rates of 36% and 45%, respectively, and an MST of 13 months at the expense of toxicities.[15] Ranimustine, an alkylating agent crossing the blood-brain barrier, and intrathecal prophylaxis with methotrexate and prednisone were incorporated because ATLL frequently involves the CNS.[4,16] Carboplatin and ranimustine were incorporated because the activity of these agents is not affected by the expression of P-glycoprotein, a product of the MDR gene *MDR1*, which is frequently expressed on ATLL cells.[17] The promising results of JCOG9303 prompted us to conduct a randomized controlled trial comparing the LSG15 regimen with biweekly CHOP against aggressive ATLL. Dose intensification of CHOP with prophylactic use of G-CSF was expected to improve survival among patients with aggressive NHL, and our randomized phase II study (JCOG9505) comparing biweekly CHOP with dose-escalated CHOP to treat aggressive NHL excluding ATLL revealed biweekly CHOP to be more promising.[18] Therefore, we regarded biweekly CHOP as a standard treatment for NHL including aggressive ATLL at the time of designing this phase III study.

PATIENTS AND METHODS

Patients

Previously untreated patients with aggressive ATLL (ie, acute-, lymphoma-, or unfavorable chronic-type ATLL) were eligible. Unfavorable chronic-type ATLL (defined by at least one of the following three factors: low serum albumin, high lactate dehydrogenase, or high blood urea nitrogen concentration) had an unfavorable prognosis similar to acute- or lymphoma-type ATLL.[6] The diagnosis of ATLL was made based on seropositivity for human T-cell lymphotropic virus type I and histologically and/or cytologically proven peripheral T-cell malignancy.

Eligibility criteria, which were identical to those for the previous studies JCOG9109 and JCOG9303, included no prior chemotherapy, age 15 to 69 years, preserved organ functions, and performance status (PS) of 0 to 3 or 4 as a result of hypercalcemia caused by ATLL.[14,15] The study protocol and the informed consent document were approved by both the JCOG Protocol Review Committee and the institutional review board of each institution.

Registration

Registration involved a telephone call or facsimile from the participating physicians to the JCOG Data Center, National Cancer Center, Tokyo, Japan. After an evaluation of eligibility, the patient was assigned to receive either modified (m) LSG15 or mLSG19 with a minimization method for balancing PS (0 or 1 *v* 2, 3, or 4) and institution.

Treatment

mLSG15 in JCOG9801 was a modified version of LSG15 in JCOG9303, consisting of the following three regimens: VCAP (vincristine 1 mg/m^2, maximum, 2 mg; cyclophosphamide 350 mg/m^2; doxorubicin 40 mg/m^2; and prednisone 40 mg/m^2) on day 1, AMP (doxorubicin 30 mg/m^2, ranimustine 60 mg/m^2, prednisone 40 mg/m^2) on day 8, and VECP (vindesine 2.4 mg/m^2 on day 15, etoposide 100 mg/m^2 on days 15 to 17, carboplatin 250 mg/m^2 on day 15, and prednisone 40 mg/m^2 on days 15 to 17) on days 15 to 17; the next course was started on day 29.[15] The modifications to mLSG15 compared with LSG15 were as follows: the total number of cycles was reduced from seven to six because of progressive cytopenia, especially thrombocytopenia, after repeating the VCAP-AMP-VECP therapy; and cytarabine 40 mg was used with methotrexate 15 mg and prednisone 10 mg for prophylactic intrathecal administration at the recovery phases of courses 1, 3, and 5 after confirmation of a platelet recovery of more than 70×10^9/L within 2 days before the next systemic chemotherapy because of the high frequency of CNS relapse in the JCOG9303 study.

mLSG19, a modified version of LSG19, consisted of eight cycles of CHOP (cyclophosphamide 750 mg/m^2; doxorubicin 50 mg/m^2; vincristine 1.4 mg/m^2, with a maximum of 2 mg, on day 1; and prednisone 100 mg on days 1 to 5) every 2 weeks.[18] The modification was an intrathecal administration identical to that in mLSG15.

Neutrophil count was checked twice a week for G-CSF use during the protocol treatment. When a serious infection occurred as a result of severe neutropenia, the doses of cyclophosphamide, doxorubicin, ranimustine, vindesine, etoposide, and carboplatin were decreased to 75% thereafter. If a second infection occurred, treatment was stopped.

Supportive Therapy

Supportive therapy for opportunistic infections was administered as in JCOG9303.[15] When the neutrophil count decreased to less than 1×10^9/L, G-CSF was administered subcutaneously every day until recovery to more than 5×10^9/L was achieved. Each course of mLSG19, VCAP in mLSG15, or AMP/VECP in mLSG15 was started after confirmation of a neutrophil count of more than 1.2×10^9/L, more than 1.0×10^9/L, or more than 0.5×10^9/L, respectively. Administration of G-CSF was discontinued on the day of chemotherapy and the day before. In cases when the hemoglobin level was less than 8 g/dL or platelet count was less than 20×10^9/L, an RBC or platelet transfusion was administered, respectively. Erythropoietin was not recommended for supportive care.

Response and Toxicity Evaluation

Response was judged using our own criteria for ATLL as described.[14,15] Toxicity was graded according to the JCOG toxicity criteria, an expanded version of the National Cancer Institute Common Toxicity Criteria version 1.0.[19]

Statistical Analysis

This trial was designed as a multicenter prospective randomized controlled trial. All analyses were performed on an intent-to-treat basis. The primary end point was overall survival (OS), and the secondary end points were progression-free survival (PFS), CR rate, and toxicity. The planned duration of accrual was 3 years, and the planned follow-up time was 2 years. The study was designed as a superiority trial, with the one-sided hypothesis according that the superiority of the control arm to the mLSG15 arm was out of concern a priori. This is because mLSG15 was expected to be associated with frequent and severe toxicities compared with the control arm.[15,18] The required sample size was 114 eligible patients in total, for 80% power to detect a hazard ratio of 0.6 under the assumption that survival times were exponentially distributed (corresponding to a 15% difference in the 3-year survival rate when the rate in the mLSG19 arm is 10%) with a one-sided type I error of 0.05. The planned sample size was 130 randomly assigned patients, with the expectation that 10% would be ineligible. The duration of accrual and the follow-up time were amended to 5 years and 1 year, respectively, in 2001 because of slow accrual.

OS was defined as the time from random assignment until death from any cause or until the last follow-up for patients who were alive. PFS was defined as the time from random assignment until death from any cause,

relapse, or progressive disease or until the last follow-up for patients who were alive. The CR rate and ORR were defined as the proportion of patients with CR and with CR or partial response, respectively, of all randomly assigned patients. Survival estimates were calculated using the Kaplan-Meier method and compared by stratified log-rank test for all randomly assigned patients, with PS as a stratification factor. An analysis of adverse events was conducted for all patients who received the protocol treatment, whether partially or completely. As a sensitivity analysis, the Cox regression was carried out. In accordance with the hypothesis, all of the *P* values are presented as one sided, except for when explicitly stated as two sided. All analyses were performed with SAS software Release 8.2 (SAS Institute, Cary, NC).

The JCOG Data Center collected and managed case report forms. In-house interim monitoring for quality control was performed at the center, and the monitoring reports were semiannually submitted to and reviewed by the JCOG Data and Safety Monitoring Committee. One interim analysis was planned after half of the planned number of patients had been off treatment with an adjustment for multiplicity by the alpha-spending function of O'Brien-Fleming.[20]

RESULTS

Patient Characteristics

Between July 1998 and October 2003, 118 patients were enrolled from 27 participating institutions (Fig 1). In June 2001, an interim analysis was performed according to the protocol and did not meet the prespecified stopping criteria ($\alpha = .00022$), and the study was continued. The final analyses were performed in February 2005 based on the follow-up data from December 2004 ($\alpha = .04992$). Fifty-seven patients were assigned to the mLSG15 arm (VCAP-AMP-VECP), and the remaining 61 patients were assigned to the mLSG19 arm (biweekly CHOP). The characteristics of the 118 patients are listed in Table 1. Two patients, one from each arm, were deemed ineligible after random assignment because they were judged to have organ dysfunctions not caused by the invasion of ATLL cells by the case report form review. Age, sex, and subtypes of ATLL were well balanced between the arms. However, there were some imbalances in prognostic factors. Although patients were stratified by PS of 0 or 1 versus 2, 3, or 4 at random assignment, there was an imbalance between PS 0 and 1. PS 0 was more frequent in the biweekly CHOP arm than the VCAP-AMP-VECP arm. Also, bulky mass (> 5 cm in diameter) was less frequent in the biweekly CHOP arm. In contrast, "B" symptoms were more frequent in the biweekly CHOP arm.

Table 1. Characteristics of Randomly Assigned Patients

Characteristic	VCAP-AMP-VECP (n = 57)* No. of Patients	VCAP-AMP-VECP (n = 57)* %	Biweekly CHOP (n = 61)* No. of Patients	Biweekly CHOP (n = 61)* %
Age, years				
Median	56		58	
Range	36-69		33-69	
Sex				
Male	27	47	34	56
Female	30	53	27	44
Subtypes of ATLL				
Acute	40	70	41	67
Lymphoma	12	21	14	23
Unfavorable chronic	5	9	6	10
PS				
0	19	33	30	49
1	27	47	19	31
2	8	14	10	16
3	2	4	2	3
4	1	2	0	0
B symptoms				
Absent	39	68	34	56
Present	18	32	27	44
Bulky mass, cm				
< 5	36	63	49	80
≥ 5	17	30	9	15
≥ 10	4	7	3	5

Abbreviations: VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone; AMP, doxorubicin, ranimustine, and prednisone; VECP, vindesine, etoposide, carboplatin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ATLL, adult T-cell leukemia-lymphoma; PS, performance status.
*Two patients, one in each arm, were ineligible because of organ dysfunction.

Response and Survival

Responses in all randomly assigned patients are listed in Table 2. The CR rate, including uncertified CR, was higher in the VCAP-AMP-

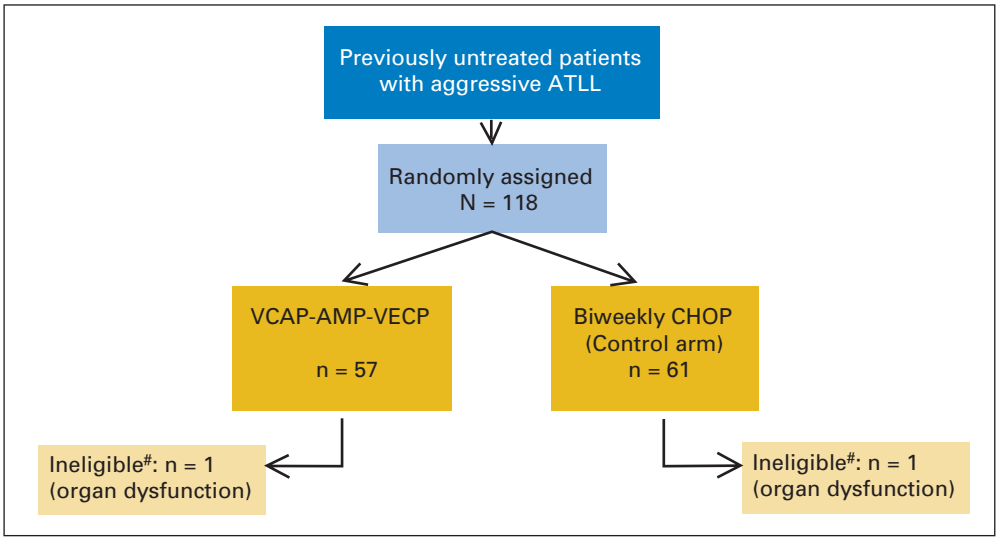

Fig 1. Enrollment and treatment of patients. (#) Included in the analysis. ATLL, adult T-cell leukemia-lymphoma; VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone; AMP, doxorubicin, ranimustine, and prednisone; VECP, vindesine, etoposide, carboplatin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 2. Response to Treatment

Response	% of Patients: VCAP-AMP-VECP (n = 57)	% of Patients: Biweekly CHOP (n = 61)	*P*
CR	40	21	
CRu	0	3	
PR	32	41	
NR	9	16	
PD	18	16	
Not assessable	2	2	
CR + CRu	40	25	.020*
95% CI	27.6 to 54.2	14.5 to 37.3	
CR + CRu + PR	72	66	NS*
95% CI	58.5 to 83.0	52.3 to 77.3	

Abbreviations: VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone; AMP, doxorubicin, ranimustine, and prednisone; VECP, vindesine, etoposide, carboplatin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CRu, unconfirmed complete response; PR, partial response; NR, no response; PD, progressive disease; NS, not significant.
*Fisher's exact test (one sided).

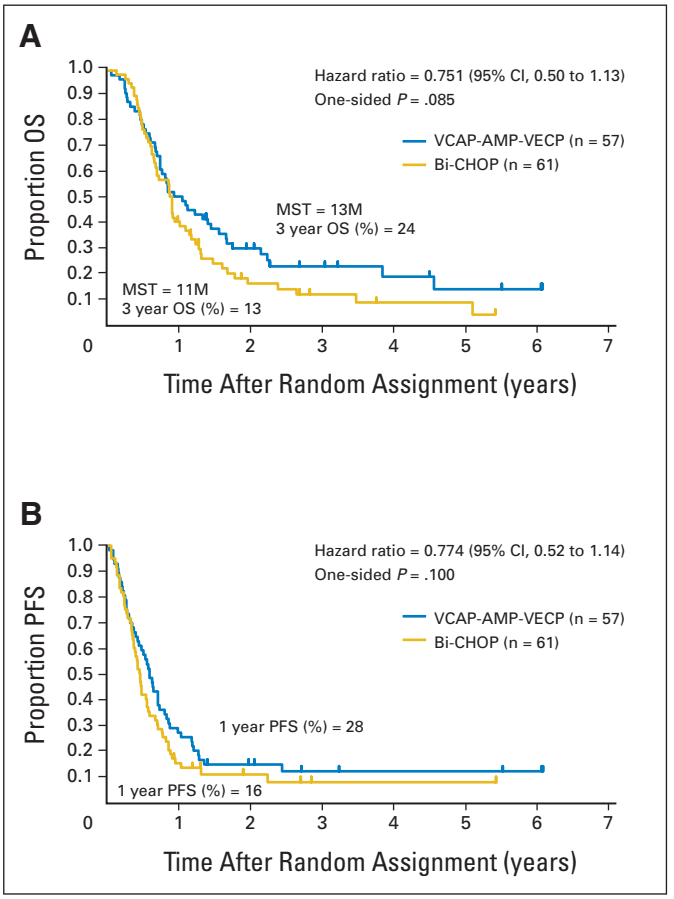

Fig 2. (A) Kaplan-Meier estimate of overall survival (OS) for all randomly assigned patients. (B) Kaplan-Meier estimate of progression-free survival (PFS) for all randomly assigned patients. VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone; AMP, doxorubicin, ranimustine, and prednisone; VECP, vindesine, etoposide, carboplatin, and prednisone; Bi-CHOP, biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone.

VECP arm (40%) than the biweekly CHOP arm (25%; $P = .020$), and ORRs were similar (72% *v* 66%, respectively) between the arms.

Median follow-up time for all randomly assigned patients was 10.9 months. The MST and OS rate at 3 years without censoring the transplantation patients were 12.7 months and 24%, respectively, in the VCAP-AMP-VECP arm and 10.9 months and 13%, respectively, in the biweekly CHOP arm (Fig 2A). For OS, the preplanned, one-sided, log-rank $P = .085$ (two-sided $P = .169$), and the hazard ratio was 0.75 (95% CI, 0.50 to 1.13). A Cox regression analysis with PS (0 *v* 1 *v* 2 to 4) as stratum for baseline hazard functions was performed to evaluate the effect on OS of the factors of age, B symptoms, subtypes of ATLL, lactate dehydrogenase, blood urea nitrogen, bulky mass, and treatment arms. According to this analysis, the hazard ratio and *P* value for the treatment arms were 0.62 (95% CI, 0.38 to 1.01) and $P = .028$ (two-sided $P = .056$), respectively. The difference between the crude analysis and this result was because of unbalanced prognostic factors, such as PS 0 versus 1, and the presence or absence of bulky lesions between the treatment arms. The median PFS time and PFS rate at 1 year were 7.0 months and 28% in the VCAP-AMP-VECP arm and 5.4 months and 16% in the biweekly-CHOP arm, respectively ($P = .100$, two-sided $P = .200$; hazard ratio = 0.77; 95% CI, 0.52 to 1.14; Fig 2B).

The rate of completion of the planned treatment was 32% in the VCAP-AMP-VECP arm and 49% in the biweekly CHOP arm. Progressive disease or relapse, as a reason for discontinuation of treatment, was observed in 40% of patients in the VCAP-AMP-VECP arm and 31% in the CHOP arm. These results seem to be associated with the periods of treatment (ie, 24 weeks in the VCAP-AMP-VECP arm and 16 weeks in the biweekly CHOP arm) because OS and PFS were better in the VCAP-AMP-VECP arm. Reasons for going off treatment, such as toxicity, were relatively numerous in the VCAP-AMP-VECP arm.

The period needed to complete each course of chemotherapy and proceed to the next course was stable in the biweekly CHOP arm (median, 15 days in courses 1 to 2 and 14 days in courses 7 to 8). In contrast, the more advanced the therapy, the more time that was required, especially after course 3 as a result of bone marrow suppression, mainly neutropenia, despite using G-CSF, in the VCAP-AMP-VECP arm (median, 30 days in courses 1 to 2 and 42 days in courses 5 to 6). The average duration of G-CSF use was 12.9 days and 5.4 days per course in the VCAP-AMP-VECP and biweekly CHOP arms, respectively.

Toxicities

Excluding one patient in the biweekly CHOP arm who refused protocol chemotherapy, 117 patients were assessable for toxicity (Table 3). The major toxicities in both arms were cytopenia and infection. In general, toxicity was more severe in the VCAP-AMP-VECP arm. In the VCAP-AMP-VECP arm versus biweekly CHOP arm, rates of grade 4 neutropenia, grade 4 thrombocytopenia, and grade 3 or 4 infection were 98% *v* 83%, 74% *v* 17%, and 32% *v* 15%, respectively. Three treatment-related deaths, two from sepsis and one from interstitial pneumonitis related to neutropenia, were reported in the VCAP-AMP-VECP arm. Two cases of myelodysplastic syndrome were reported, one each in both arms.

Subgroup Analysis

As shown in Figure 3, there was interaction between the treatment arms and PS, which suggests that the intensive

Table 3. Hematologic and Nonhematologic Toxicities in 117 Treated Patients

Toxicity	Grade	% of Patients: VCAP-AMP-VECP (n = 57)	% of Patients: Biweekly CHOP (n = 60)
Neutropenia	4	98	83
Thrombocytopenia	4	74	17
T-bilirubin	3 + 4	5	2
ALT	3 + 4	11	5
Hyperglycemia	3 + 4	13	4
Hyponatremia	3 + 4	5	5
Hypokalemia	3 + 4	12	2
Stomatitis	3 + 4	7	2
Dyspnea	3 + 4	7	5
Infection	3 + 4	32	15
Neuropathy	3 + 4	2	7
Treatment-related deaths, No.	—	3*	0

Abbreviations: VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone; AMP, doxorubicin, ranimustine, and prednisone; VECP, vindesine, etoposide, carboplatin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.
*Two patients died of sepsis, and one died of interstitial pneumonitis.

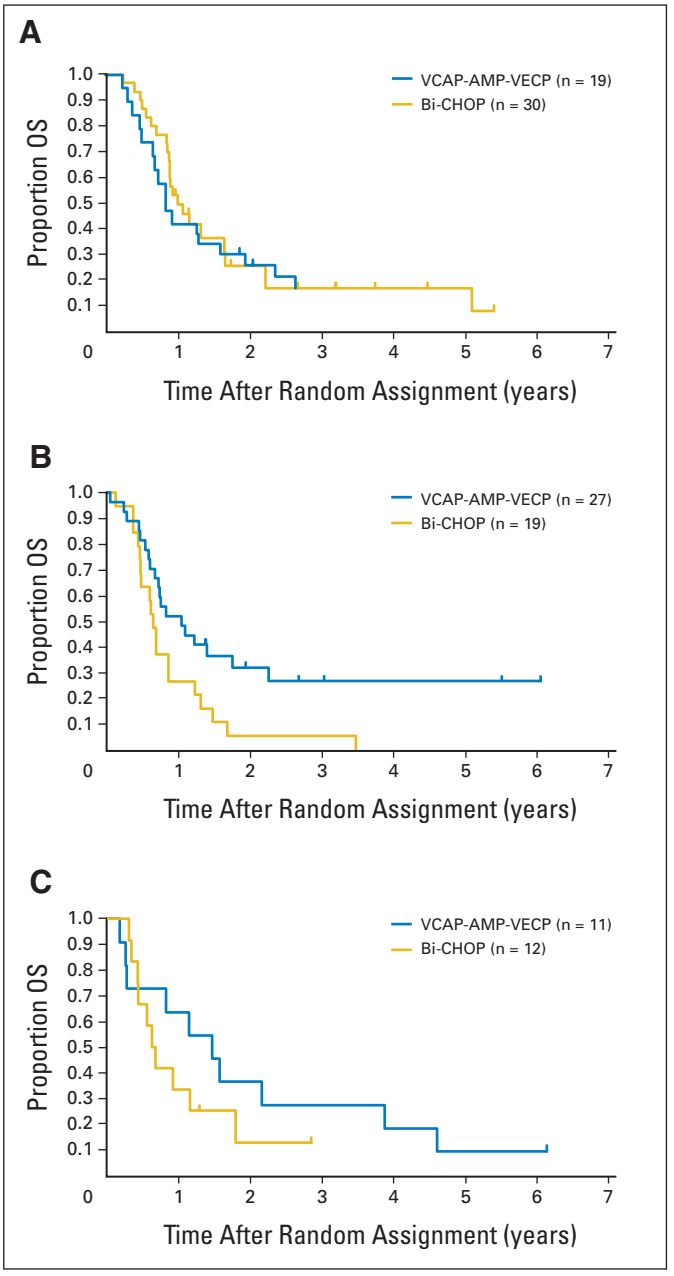

Fig 3. Kaplan-Meier estimate of overall survival (OS) for all randomly assigned patients according to performance status (PS) at diagnosis: (A) PS of 0; (B) PS of 1; and (C) PS of 2, 3, or 4. VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone; AMP, doxorubicin, ranimustine, and prednisone; VECP, vindesine, etoposide, carboplatin, and prednisone; Bi-CHOP, biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone.

VCAP-AMP-VECP regimen is more likely to benefit patients with a poor PS, possibly reflecting a more advanced stage of ATLL. Similarly, the younger population was more likely to benefit from VCAP-AMP-VECP (Fig 4). In contrast, no such interaction was observed in the analysis concerning disease type and bulky tumor (data not shown). Fourteen patients, seven in each group, received allogeneic hematopoietic stem-cell transplantation (alloHSCT). Four and three patients received the transplantation before progressive disease in the VCAP-AMP-VECP arm and biweekly CHOP arm, respectively. The estimated OS rates at 2 years for patients receiving alloHSCT were similar (43% for both arms).

DISCUSSION

To our knowledge, this trial, JCOG9801, comparing the efficacy and safety of VCAP-AMP-VECP and biweekly CHOP, is the first phase III trial exclusively conducted for ATLL in the world. We found a better OS in patients with aggressive ATLL treated with VCAP-AMP-VECP compared with biweekly CHOP, as well as a higher CR rate and longer PFS. Although the primary analysis of OS failed to show statistical significance (hazard ratio = 0.75, $P = .085$), a sensitivity analysis demonstrated the consistent result even after an adjustment of imbalance in baseline prognostic factors (hazard ratio = 0.62, $P = .028$). We consider the longer OS at 3 years and higher CR rate of VCAP-AMP-VECP than biweekly CHOP in this trial to be clinically meaningful and the former to be recommended as the first choice for patients with this disease despite higher toxicities.

Hematologic toxicity and infections were more frequent in the VCAP-AMP-VECP arm than the biweekly CHOP arm, which are similar findings to the previous JCOG9303 study with the original VCAP-AMP-VECP regimen.[15] Although both regimens were supported with G-CSF, four more drugs were incorporated in VCAP-AMP-VECP compared with biweekly CHOP, with a dose-dense and long period of chemotherapy. Three treatment-related deaths, which were related to severe neutropenia despite using G-CSF, were reported in the VCAP-AMP-VECP arm. Although VCAP-AMP-VECP caused remarkable thrombocytopenia, no serious hemorrhagic events were documented, possibly because platelet transfusion was encouraged without modifying the schedule of chemotherapy based on the decrease in the platelet count. ATLL patients treated with VCAP-AMP-VECP should be carefully monitored for complications, especially cytopenia and infections,

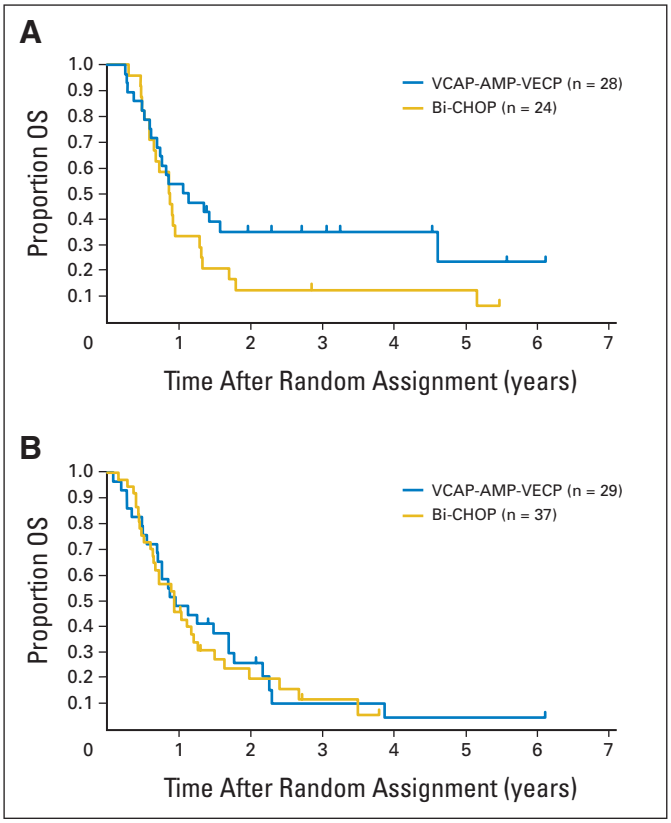

Fig 4. Kaplan-Meier estimate of overall survival (OS) for all randomly assigned patients according to age at diagnosis: (A) age < 56 years and (B) age ≥ 56 years. VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone; AMP, doxorubicin, ranimustine, and prednisone; VECP, vindesine, etoposide, carboplatin, and prednisone; Bi-CHOP, biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone.

with supportive care such as platelet transfusion, use of G-CSF, and the prophylaxis of opportunistic infection.[4-7]

Because of the geographically limited distribution and rarity of this disease, large-scale trials for the treatment of ATLL have rarely been performed. There have been trials of intensive chemotherapy and a unique combination chemotherapy consisting of interferon alfa and zidovudine.[21,22] However, the results were inferior to those of VCAP-AMP-VECP.[23] The following factors might explain the reasons for the superiority of VCAP-AMP-VECP compared with biweekly CHOP against aggressive ATLL. Four more drugs were incorporated in the VCAP-AMP-VECP arm, compared with the biweekly CHOP arm, with a dose-dense and long period of chemotherapy. Furthermore, carboplatin and ranimustine were incorporated, and these agents are not affected by P-glycoprotein, which is frequently expressed in ATLL cells at onset.[17]

According to the results of subgroup analyses, VCAP-AMP-VECP may be more beneficial in patients with more advanced ATLL or in younger patients. However, because this study excluded patients with a PS of 4 not caused by hypercalcemia, the results would not be applicable to patients with a PS of 4 caused by an opportunistic infection or organ involvement by ATLL.

Our previous studies in advanced NHL revealed that CR rate and OS were poorer in ATLL than in other aggressive NHL.[10-12] In the recent two studies, biweekly CHOP was better than or not inferior to standard CHOP for aggressive NHL excluding ATLL.[24,25] VCAP-AMP-VECP was superior to biweekly CHOP for ATLL in this study. A G-CSF–supported dose-intensified regimen with carboplatin and ranimustine might have overcome the characteristics of ATLL cells, such as rapid proliferation and P-glycoprotein expression.

AlloHSCT is now considered as promising for the treatment of young patients with ATLL.[26] Thus, despite higher toxicities and poor completion rate of the planned course of therapy, VCAP-AMP-VECP, which provided a higher CR rate and a probable survival advantage, is promising as induction chemotherapy preceding upfront alloHSCT for aggressive ATLL. However, to prove the effectiveness of this strategy, further studies are needed.

In conclusion, the results of the present phase III study suggest that VCAP-AMP-VECP is a more effective chemotherapy regimen for patients with newly diagnosed aggressive ATLL even with higher toxicity profiles. However, the MST of 13 months is still not satisfactory. We are now planning a phase II study of myeloablative alloHSCT after induction therapy with VCAP-AMP-VECP for young patients with this disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Acknowledgment

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).