Fig. 4. (a) Overall and (b) event-free survival according to the mean daily dose during the first 24 months per body weight. The cut-off value was set at >5.0 mg/day/kg (e.g. if a patient whose body weight was <60 kg received imatinib at a mean daily dose of 300 mg).

Table 5. Number of patients and survival according to the mean daily dose of imatinib during the first 24 months per body weight

| | Mean daily dose/body weight (mg/day/kg) | | | | |
| | >5.0† | | ≤5.0 | | |
	Actual bodyweight (kg)	No. patients	Actual bodyweight (kg)	No. patients	P-value
Imatinib daily dose group‡					
400 mg	<80	266	≥80	28	
300 mg	<60	63	≥60	27	
200 mg	<40	5	≥40	62	
Estimated 7-year OS	96%		89%		0.0012
Estimated 7-year EFS	88%		76%		0.0016

†The cut-off value was set at >5.0 mg/day/kg (e.g. the mean daily dose of imatinib during the first 24 months (300 mg) divided by body weight [<60 kg]). ‡Mean daily doses in the 400-, 300-, and 200-mg groups were ≥360, 270–359, and <270 mg imatinib, respectively. Patients who discontinued imatinib were not included in the analysis. EFS, event-free survival; OS, overall survival.

to the mean daily dose during the first 6, 12, and 24 months of treatment. The rate of achieving CCyR or MMR differed significantly between the 300- and 400-mg groups during the first 24 months. Even so, there were no significant differences in OS, PFS, and EFS between the 300- and 400-mg groups during the first 6, 12, or 24 months of treatment. Conversely, the 200-mg group showed markedly inferior cytogenetic and/or molecular responses, as well as inferior survival, compared with the 300- and 400-mg groups. We also analyzed outcomes according to the mean daily dosage during the first 24 months per BW, with the results suggesting that patients who had relatively high daily dosage per BW were likely to have better OS and EFS even though the actual daily dose had been lower than 400 mg imatinib. The OS and EFS in the 300-mg group in the present study were not inferior compared with rates reported in the IRIS study (85% at 7 years vs. 83% at 6 years), which suggests that a considerable number of Japanese patients who received doses lower than 400 mg demonstrated an adequate response. A prospective comparative study would be necessary to confirm this observation.

Two recent studies showed a correlation between the plasma trough levels (C_{min}) and response, suggesting that maintaining C_{min} above approximately 1000 ng/mL was associated with improved outcomes.[22,23] In the present study, the mean daily dose was 331 ± 108 mg during the first 24 months and the relatively high dosage of imatinib per BW was associated with better OS and EFS, whereas in the IRIS study the mean daily dose among the patients who continued receiving imatinib was 382 ± 50 mg.[1] On the basis of our results, we assume that

the relatively small body size of Japanese patients compared with their Western counterparts may have affected C_{min}, although differences in the metabolism of imatinib because of ethnicity cannot be ruled out either. Therefore, we measured the C_{min} of imatinib in a group of patients who had received imatinib continuously at a daily dose of either 300 or 400 mg. The patients from whom blood samples were collected showed almost similar background characteristics to the entire study population. There was no significant difference in the mean C_{min} between patients receiving 300 or 400 mg imatinib, and there was no significant difference in the ratio of patients whose C_{min} was higher than 1000 ng/mL between the two groups. When pharmacokinetic analyses of patients receiving 400 mg imatinib in the present study are compared with the IRIS study, the C_{min} in the present study was distributed at higher concentrations than in the IRIS study (mean C_{min} 1165 vs. 979 ng/mL, respectively); however, the distribution of C_{min} in patients receiving 300 mg imatinib was similar between the studies.[23] Larson et al. reported a weak correlation between C_{min} and age, BW, or BSA in the IRIS study, but also suggested that the effects of body size and age on C_{min} were not likely to be of clinical significance because C_{min} showed large interpatient variability.[23] However, the C_{min} in their female patients was significantly higher than that in male patients, and they speculated that this may be due to the small body size of the female patients. The same tendency was seen in the present study, especially in terms of age and gender. Therefore, a small body size among Japanese old and/or female patients may partly account for the higher C_{min} of imatinib. Regarding

Table 6. Patient characteristics and plasma trough levels of imatinib according to the daily dose of imatinib

	Imatinib daily dose†		P-value
	400 mg	300 mg	
No. patients	26	24	
No. men/women	19/7	12/12	0.092
Age (years)	49 (17–79)	58 (33–76)	0.012
Body weight (kg)	65.2 ± 10.6	59.5 ± 10.7	0.062
BSA (m²)	1.68 ± 0.17	1.57 ± 0.17	0.034
Sokal risk group (n)			
Low	18	13	0.357
Intermediate	6	6	
High	2	5	
C_{min} (ng/mL)			
Mean ± SD	1165 ± 445	1113 ± 426	0.673
Median (range)	1035 (710–2420)	1130 (439–2140)	
% Patients on >1000 ng/mL imatinib	57.7 (15/26)	62.5 (15/24)	0.1
Best response (%)			
MCyR	26 (100)	23 (96)	
CCyR	26 (100)	22 (92)	
MMR	24 (92)	23 (96)	

Unless indicated otherwise, data are given as the mean ± SD, as the median with the range given in parentheses, or as the number of patients in each group with percentages given in parentheses, as appropriate. †Imatinib at a daily dose of 400 or 300 mg without any dose modification. BSA, body surface area; CCyR, complete cytogenetic response; C_{min}, plasma trough level; MCyR, major cytogenetic response; MMR, major molecular response.

the plasma concentration of imatinib in Japanese patients, there are other reports showing sufficient C_{min} in patients receiving imatinib at doses lower than 400 mg,[6,24] but it remains uncertain whether there are any individual or ethnic differences in the metabolism of imatinib.[24,25]

Another possible reason for the satisfactory outcomes seen for patients in the 300-mg group could be that, at this dose, imatinib could be administered continuously to some patients without serious adverse events. A recent study regarding imatinib dosage in Japanese patients reported that, based on multivariate analysis, older age and lower BW are significant risk factors for the discontinuation of imatinib therapy and that patients with these factors were less likely to achieve a CCyR.[18] Continuous and adequate dosage is essential for optimal outcome, and adherence to imatinib therapy is critical.[26,27]

In conclusion, the long-term follow-up of the JALSG CML202 study revealed almost similar excellent outcomes to those of the IRIS study and others. There were no significant differences in OS and EFS between the 300- and 400-mg imatinib groups. However, cumulative rates of cytogenetic or molecular responses in the 300-mg group were inferior to those in the 400-mg group. The results of the present study suggest that imatinib at a dose of 400 mg may be optimal for Japanese patients, but that 400 mg imatinib is not tolerable in a considerable number of patients, and that the measurement of C_{min} is useful in finding the optimal dose, especially in elderly and/or female patients. Nevertheless, excessive dose reductions to <300 mg imatinib should be avoided even in patients who are intolerant to 400 mg imatinib or have a small body size. We hope our findings are useful for the treatment of CML patients in other Asian countries.

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Disclosure Statement

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Correlation between Amp-CMLTM (FUJIREBIO Inc., Tokyo, Japan) and Fusion Quant M-BCRTM (Ipsogen, Marseille, France).

Data S1. Measurement of major *BCR-ABL1* transcript.

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Role of chemotherapy in treatments for biliary tract cancer

Junji Furuse · Akiyoshi Kasuga · Atsuko Takasu ·
Hiroshi Kitamura · Fumio Nagashima

Abstract The purpose of chemotherapy in patients with advanced solid cancers, including biliary tract cancer, is generally to improve the survival and quality of life of the patients. Also, adjuvant chemotherapy is expected to increase the curability of surgery in patients scheduled to undergo surgery. Most patients with unresectable biliary tract cancer develop obstructive jaundice, and biliary drainage is needed before any of the aforementioned treatments. Once jaundice is resolved by stenting of the bile duct or bilio-intestinal bypass, cholangitis often develops, leading to rapid deterioration of the patient's general condition. Therefore, the beneficial effect of chemotherapy in such patients remains controversial. A few randomized controlled trials have demonstrated the survival benefit of chemotherapy as compared with supportive care. In one of these trials, improvement of the quality of life was also confirmed. Recently, since the survival benefit of combined gemcitabine plus cisplatin therapy over gemcitabine alone has been demonstrated in randomized controlled clinical trials, this combined regimen has been recognized as a standard therapy for unresectable biliary tract cancer. A second-line regimen is now expected to be established for patients with gemcitabine-refractory biliary tract cancer, although the significance of second-line therapy remains unclear. One of the next issues in relation to chemotherapy for biliary tract cancer is the development of molecular-targeted agents; however, few large clinical trials of such agents have been conducted for biliary tract cancer. Various issues in chemotherapy for biliary tract cancer remain to be investigated, and global cooperation is necessary to conduct large clinical trials.

Keywords Biliary tract cancer · Chemotherapy · Survival benefit · Quality of life · Gemcitabine · Cisplatin

Introduction

Biliary tract cancer is a common cause of cancer-related death in Asia, including Japan, and Latin America. In Japan, the mortality is estimated to be 17,000 deaths annually. While surgery remains the only potentially curative treatment, the curative resection rate remains low, at approximately 40% [1]. Most patients, furthermore, develop recurrence even after curative surgery. The poor prognosis is due to the difficulty in the diagnosis of biliary tract cancer in the earlier stages and the lack of satisfactory treatments for advanced disease.

Biliary tract cancer consists of cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer; intrahepatic cholangiocarcinoma is also often included in clinical trials of treatments for biliary tract cancer. Each of these types of cancer has characteristic features and the treatment strategies and prognoses also differ. This heterogeneity has made it difficult to evaluate the efficacy of chemotherapy for biliary tract cancer, and randomized controlled trials (RCTs) with an appropriate stratification strategy, including by the tumor type, are required. Recently, a large RCT comparing combined gemcitabine plus cisplatin therapy with gemcitabine treatment alone demonstrated a survival benefit of the combined regimen over gemcitabine alone [2]. As a result, combined gemcitabine plus cisplatin therapy has come to be recognized as standard therapy for unresectable biliary tract cancer.

J. Furuse (✉) · A. Kasuga · A. Takasu · H. Kitamura ·
F. Nagashima
Department of Internal Medicine, Medical Oncology,
Kyorin University School of Medicine, 6-20-2 Shinkawa,
Mitaka, Tokyo 181-8611, Japan
e-mail: jfuruse@ks.kyorin-u.ac.jp

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The purpose of chemotherapy in patients with advanced solid cancers, including biliary tract cancer, is generally to improve their survival and quality of life (QOL), and not to achieve a cure. Also, adjuvant chemotherapy is expected to increase the curability of surgery in patients scheduled to undergo surgery. There are some difficulties in the chemotherapy of patients with biliary tract cancer. Most patients present with obstructive jaundice at diagnosis, and biliary drainage is generally needed before any of the aforementioned treatments. Once the jaundice has been resolved by stenting of the bile duct or bilio-intestinal bypass, cholangitis often develops, resulting in rapid deterioration of the patient's general condition. Thus, the beneficial effect of chemotherapy for patients with unresectable biliary tract cancer remains controversial.

In this review, based on the recent advances in chemotherapy for biliary tract cancer, the significance and roles of systemic chemotherapy for patients with unresectable biliary tract cancer are discussed.

Improvement of survival in patients with unresectable biliary tract cancer

To assess the efficacy of chemotherapy in patients with advanced biliary tract cancer, some small RCTs comparing it with supportive treatment alone have been conducted (Table 1) [3–5]. Glimelius et al. [3] reported a comparative study between chemotherapy and supportive care in 90 patients with unresectable pancreatic cancer and biliary tract cancer. In this study, 5-fluorouracil (5-FU) + leucovorinor 5-FU + leucovorin + etoposide was compared with supportive care. For all the patients, the overall survival was significantly longer in the chemotherapy group than in the supportive care group (median 6.0 vs. 2.5 months, $P < 0.01$). In only the patients with biliary tract cancer, no significant difference in survival between the two groups was noted, due to the small number of patients (37 patients), and the survival in the two groups was similar (6.5 months in the chemotherapy group and 2.5 months in the supportive care group; $P = 0.1$). Takada et al. [4] conducted a comparative study in Japan comparing 5-FU + doxorubicin + mitomycin C (FAM) with palliative treatment, such as bypass, in patients with unresectable pancreatic cancer, gallbladder cancer, and bile duct cancer. No improvement in the prognosis was demonstrated in either treatment group overall, but longer survival was achieved in the chemotherapy group than in the control group for the 18 patients with gallbladder cancer (median 5.16 months in the chemotherapy arm and 2.4 months in the control arm).

Recently, a comparative study of modified gemcitabine/oxaliplatin (Gemox), 5-FU/folinic acid (FA),and best supportive care was reported in patients with unresectable

gallbladder cancer [5]. The modified Gemox regimen yielded a statistically significantly higher response rate, progression-free survival, and overall survival as compared with 5-FU/FA chemotherapy and best supportive care. Although these studies included only a small number of patients, these results suggest a survival benefit of chemotherapy in patients with unresectable biliary tract cancer and adequate organ and bone marrow function, as long as obstructive jaundice and cholangitis can be controlled.

Promising agents for biliary tract cancer were examined in retrospective studies before a large RCT was conducted. In a pooled analysis of 104 phase II studies, significant correlations of the response rate and tumor control rate with the survival times were observed, and the response rate and tumor control rate were highest in the patients treated with a gemcitabine–platinum combination [6]. Four hundred thirteen consecutive patients administered non-surgical treatments were reviewed in a Japanese retrospective study [7]. To clarify the impact of systemic chemotherapy on the survival and identify promising agents for biliary tract cancer, the hazard ratios and 95% confidence intervals (CI) were estimated by Cox regression by subgroup of chemotherapeutic regimen as compared with best supportive care. The median overall survival in the best supportive care group was 3.12 months and that in the chemotherapy group was 7.38 months, and a statistically significant difference in survival was noted between the two groups ($P = 0.0001$). The adjusted hazard ratio in the Cox regression model using confounders for gemcitabine was 0.53 (95% CI 0.34–0.82) and for cisplatin -based regimens it was 0.49 (95% CI 0.36–0.99). Thus, gemcitabine and platinum were identified as promising agents for the treatment of biliary tract cancer.

A randomized phase II study (ABC-01) comparing gemcitabine alone with gemcitabine plus cisplatin was conducted in the United Kingdom [8]. It demonstrated superior 6-month progression-free survival (57.1 vs. 45.5%) with acceptable toxicity in the gemcitabine 1,000 mg/m^2 plus cisplatin 25 mg/m^2 group as compared with that in the gemcitabine 1,000 mg/m^2-alone group, and was therefore expanded to a phase III study (ABC-02). The results revealed a statistically significant improvement in the overall survival in the gemcitabine-plus cisplatin group as compared with that in the gemcitabine-alone group (Table 2) [2]. The BT-22 study was planned in Japan following the promising results of the ABC-01 study, and results similar to those of the ABC-02 study were demonstrated in Japanese patients with biliary tract cancer (Table 2) [9].

Improvement of the quality of life

It is difficult to assess efficacy based on the QOL, especially in patients with biliary tract cancer, because there are

Table 1 Trials comparing chemotherapy and supportive care in patients with unresectable biliary tract cancer

	n	Median OS (months)	P value	References
5-FU/leucovorin or 5-FU/leucovorin/etoposide	47	6	<0.01	Glimelius et al. [3]
Supportive care	43	2.5		
5-FU/doxorubicin/mitomycin C	42	4.96	0.283	Takada et al. [4]
Control	41	4.7		
Gemcitabine/oxaliplatin	27	9.5	0.039	Sharma et al. [5]
5-FU/folinic acid	28	4.6		
Best supportive care	27	4.5		

5-FU fluorouracil, *OS* overall survival

Table 2 Efficacy of first-line chemotherapy for unresectable biliary tract cancer

Regimen	n	Response rate (%)	Median PFS (months)	Median OS (months)	References
Gemcitabine	206	15.5	5.0	8.3	Valle et al. [2]
Gemcitabine/cisplatin	204	26.1	8.0	11.7	
Gemcitabine	42	11.9	3.7	7.7	Okusaka et al. [9]
Gemcitabine/cisplatin	41	19.5	5.8	11.2	
Gemcitabine/capecitabine	45	32	6.0	14.0	Cho et al. [13]
Gemcitabine/capecitabine	75	29	6.2	12.7	Riechelmann et al. [14]
Gemcitabine/capecitabine	44	25	7.2	13.2	Koeberle et al. [15]
Gemcitabine/S-1	35	34.3	5.9	11.6	Sasaki et al. [16]

PFS progression-free survival, *OS* overall survival

many specific symptoms due to tumor progression and/or obstruction of the bile duct in patients with advanced biliary tract cancer. In the ABC-02 study, it was demonstrated that patients who received gemcitabine had a significantly increased incidence of grade 3 or 4 liver function test abnormalities, possibly as a result of inferior disease control and biliary drainage as compared with that in the group administered combined gemcitabine plus cisplatin therapy [2]. This finding suggests that a higher efficacy of chemotherapy against tumor progression in patients with biliary tract cancer might contribute to maintaining the patency of the bile duct and prevent cholangitis due to re-obstruction of the bile duct.

Improvement in the QOL was also examined in a trial comparing chemotherapy and supportive care, with QOL assessed by using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) version 1.0 questionnaire [3]. The results revealed a significant QOL improvement in the chemotherapy group (P < 0.01); a 36% improvement was observed in the chemotherapy group (pancreatic cancer 38%, biliary tract cancer 33%) and a 10% (pancreatic cancer 13%, biliary tract cancer 5%) improvement was shown in the supportive care group. In the analysis by symptom, significant improvements of pain, fatigue, appetite, and dyspnea after 2 months, and that of pain and dyspnea after 4 months were observed in the chemotherapy group.

Second-line therapy for unresectable biliary tract cancer

Now that first-line chemotherapy has been established, the development of a second-line therapy would be the next logical step to improve survival in patients with unresectable biliary tract cancer. New oral fluoropyrimidines, such as capecitabine and tegafur/gimeracil/oteracil potassium (S-1), which are prodrugs of FU, have been investigated as monotherapy or in combination with gemcitabine. There are few prospective clinical trials that have focused on second-line therapy only in patients with biliary tract cancer. S-1 was investigated in patients with gemcitabine-refractory biliary tract cancer in a phase II study [10]. There were 3 confirmed partial responses (7.5%) among the 40 patients assessed, and 22 patients (55%) with stable disease. The median progression-free and overall survivals were 2.5 and 7.5 months, respectively. Despite the acceptable toxicity of S-1, its efficacy was modest, and these results could serve as reference data for the development of second-line therapy.

The impact of second-line therapy after gemcitabine-based chemotherapy was assessed in the ABC-02 and BT-22 studies [11]. In the ABC-02 trial conducted in the United Kingdom, the treatment of patients with disease progression was left to individual clinicians' discretion, and was best supportive care for the majority, with only

17% of patients receiving further chemotherapy, mostly 5-FU-based chemotherapy. On the other hand, in the BT-22 study conducted in Japan, 73% of the patients in the gemcitabine-plus-cisplatin group and 78% of the patients in the gemcitabine-alone group received post-study chemotherapy. S-1 was approved for the treatment of biliary tract cancer based on the results of a first-line phase II study in Japan [12], and, consequently, more than 60% of the patients in the BT-22 study were treated with S-1 as second-line therapy [9]. This difference in the rate of application of second-line therapy could have potentially improved the overall survival in the BT-22 study as compared with that in the ABC-02 study, although the overall survival in the two studies was quite similar. So far, therefore, the impact of second-line therapy in patients with gemcitabine-refractory biliary tract cancer remains unclear.

Future perspectives on chemotherapy for unresectable biliary tract cancer

Gemcitabine has been recognized as a key drug for the treatment of biliary tract cancer, and many phase II studies of gemcitabine have been conducted. The combination of gemcitabine plus the oral fluoropyrimidines capecitabine or S-1 also showed promising activity in phase II studies. These phase II studies yielded response rates of 25–34% and a median overall survival of 11.6–14.0 months (Table 2) [13–16]. A randomized phase II study comparing combined gemcitabine plus S-1 chemotherapy and S-1 monotherapy was conducted by the Japanese Clinical Oncology Group (JCOG) to evaluate the efficacy and safety of the two regimens and to determine which was the more promising regimen as a test arm regimen for comparison with the current standard regimen; namely, gemcitabine plus cisplatin [17]. If the combination of gemcitabine plus S-1 is found to be promising, a large RCT comparing this combination with gemcitabine plus cisplatin would be warranted.

One of the next issues that need to be addressed is whether molecular-targeted agents might also exert activity against biliary tract cancer. To date, no large clinical trials of molecular-targeted agents have been conducted for biliary tract cancer; however, some of these agents appear to offer promise. A combination of Gemox plus bevacizumab, a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), yielded promising results in a phase II study, with a response rate of 40% and median overall survival of 12.7 months [18]. A phase II study of Gemox plus cetuximab, an anti-epidermal growth factor receptor (EGFR) antibody, also demonstrated promising efficacy, with a response rate of 63% and

median overall survival of 15.2 months [19]. A randomized phase II study comparing Gemox plus cetuximab and Gemox alone has been conducted in France [20], and has been expanded to a phase III study.

Usage of monotherapy with targeted agents as second-line chemotherapy is also expected. Some preclinical experiences show that VEGF receptor or EGFR inhibitors administered alone may exert efficacy against biliary tract cancer. In many patients with progressive disease receiving first-line chemotherapy with the relatively toxic regimen of gemcitabine plus cisplatin or Gemox, the general condition may be poor, and serious cholangitis can easily develop. Less toxic therapy, such as monotherapy with a targeted agent, may be useful in such patients.

Conclusions

Effective chemotherapy is necessary to improve the survival and QOL of patients with biliary tract cancer. Because biliary tract cancer is a relatively rare disease as compared with other gastrointestinal cancers, such as colorectal cancer or gastric cancer, large clinical trials of treatments for this cancer are difficult to conduct. Efforts to establish new standard chemotherapies are ongoing, and international collaboration is necessary for the success of these efforts.

Conflict of interest The authors declare that they have no conflict of interest.

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Phase II/III Study of R-CHOP-21 Versus R-CHOP-14 for Untreated Indolent B-Cell Non-Hodgkin's Lymphoma: JCOG 0203 Trial

Takashi Watanabe, Kensei Tobinai, Taro Shibata, and Takashi Terauchi, National Cancer Center Hospital; Kengo Takeuchi, Japanese Foundation for Cancer Research; Shigeru Nawano, International University of Health and Welfare Mita Hospital, Tokyo; Kunihiro Tsukasaki, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Science, Nagasaki; Yasuo Morishima, Aichi Cancer Center Hospital; Tomohiro Kinoshita, Nagoya University Graduate School of Medicine; Michinori Ogura, Nagoya Daini Red Cross Hospital; Tomomitsu Hotta, National Hospital Organization Nagoya Medical Center, Nagoya; Nobuo Maseki, Saitama Cancer Center, Ina; Takayo Suzuki, Shiga Medical Center for Adults, Moriyama; Motoko Yamaguchi, Mie University Graduate School of Medicine, Tsu; Kiyoshi Ando, Tokai University School of Medicine, Isehara; Masafumi Taniwaki, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto; and Naokuni Uike, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan.

Takashi Watanabe, Kensei Tobinai, Taro Shibata, Kunihiro Tsukasaki, Yasuo Morishima, Nobuo Maseki, Tomohiro Kinoshita, Takayo Suzuki, Motoko Yamaguchi, Kiyoshi Ando, Michinori Ogura, Masafumi Taniwaki, Naokuni Uike, Kengo Takeuchi, Shigeru Nawano, Takashi Terauchi, and Tomomitsu Hotta

ABSTRACT

Purpose

Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is one of the most effective front-line therapies to treat indolent B-cell lymphoma. Granulocyte colony-stimulating factor (G-CSF), which potentiates antibody-dependent rituximab cytotoxicity, is used to shorten CHOP intervals. To improve progression-free survival (PFS) in patients treated with R-CHOP as the primary end point, we conducted a phase III study.

Patients and Methods

Patients with untreated stages III to IV indolent B-cell lymphoma were randomly assigned to six cycles of R-CHOP every 3 weeks (R-CHOP-21) or every 2 weeks (R-CHOP-14) with G-CSF. Maintenance rituximab was not allowed.

Results

Three hundred patients were enrolled. At the median follow-up time of 5.2 years, there was no significant difference in PFS between arms for the 299 eligible patients; the median was 3.7 (R-CHOP-21) v 4.7 (R-CHOP-14) years, 57% v 58% at 3 years, and 41% v 43% at 6 years, respectively (hazard ratio [HR], 0.92; 95% CI, 0.68 to 1.25; one-sided $P = .30$). The median overall survival (OS) time was not reached in either arm, and there was no significant difference (6-year OS: 87% [R-CHOP-21] v 88% [R-CHOP-14]; HR, 1.15; 95% CI, 0.57 to 2.30; one-sided $P = .65$). Although grade 4 neutropenia and grade 3 infections were more frequent in the R-CHOP-21 group, R-CHOP was feasible in both arms.

Conclusion

The R-CHOP dose-dense strategy failed to improve PFS of patients with untreated indolent B-cell lymphoma. Further improvement of first-line treatment or investigations on postremission therapy following R-CHOP should be explored.

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INTRODUCTION

In randomized clinical trials (RCTs), rituximab in combination with chemotherapy has been shown to improve the outcome for patients with previously untreated, advanced-stage follicular lymphoma (FL) relative to combination chemotherapy alone.[1,2] Currently, rituximab with chemotherapy is used as the standard therapy for most patients with FL. Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is regarded as one of the most effective first-line treatments for indolent B-cell non-Hodgkin's lymphoma

(NHL).[1,3,4] Currently, there is no standard therapy for advanced-stage indolent B-cell NHL and FL grade 3B. A first-line intensive chemotherapy regimen has been shown to cause durable remission in patients with indolent B-cell NHL,[5] although there is no evidence to suggest that dose-intensified chemotherapy led to prolonged survival of the patients in the pre-rituximab era.[6] It is currently unknown whether a dose-dense strategy can improve the outcome for patients with indolent B-cell NHL who receive R-CHOP. A short interval of rituximab administration can achieve a higher serum concentration and, consequently, a better antitumor

response.[7,8] Furthermore, the clinical utility of any immunomodulators has not yet been evaluated in RCTs. Granulocyte colony-stimulating factor (G-CSF) has often been used to shorten CHOP intervals,[9-12] and it potentiates the antibody-dependent cell-mediated cytotoxicity of rituximab.[13,14]

In this prospective trial, we attempted to determine whether patients with indolent B-cell NHL would have long-term benefits from dose-dense immunochemotherapy.

PATIENTS AND METHODS

Study Design

We considered whether R-CHOP-21 (R-CHOP administered every 3 weeks) could be used as a putative standard first-line therapy for indolent B-cell NHL. In addition, R-CHOP-14 (R-CHOP administered every 2 weeks with G-CSF) was selected as a promising therapeutic strategy for the future. However, there was no available evidence to support using either of those rituximab-containing therapies as the treatment arm of an RCT. An RCT comparing the two treatments should be planned after R-CHOP-21 is confirmed to be the standard of care for patients with advanced-stage indolent B-cell NHL from the preceding RCT results. Moreover, the incidence of FL is low in Japan.[15,16] We therefore designed this clinical trial as a phase II/III study to confirm the necessary efficacy and feasibility of R-CHOP-21 or R-CHOP-14 versus a non–rituximab-containing regimen during phase II. Furthermore, these phase II patients would be included in the analysis of phase III.

Patient Selection

Patients with previously untreated stage III to IV indolent B-cell NHL and FL grade 3B were randomly assigned by using a minimization method to receive six cycles of either R-CHOP-21 (arm A) or R-CHOP-14 (arm B).

Age, bulky disease, and institution were used as dynamic allocation adjustment factors.

The major eligibility criteria were as follows: age 20 to 69 years; CD20^{+} histologically confirmed indolent B-cell NHL, including grades 1 to 3 FL, according to the 2001 WHO classification[17]; stage III or IV disease; an Eastern Cooperative Oncology Group performance status of 0 to 2; at least one measurable lymphomatous lesion more than 1.5 cm detected by computed tomography (CT); and adequate organ function. Patients were excluded if they had histologic transformation to aggressive lymphoma, more than 10 × 10⁹/L circulating CD20^{+} lymphoma cells, hepatitis B virus (HBV) surface antigens or antibodies to hepatitis C virus, glaucoma,[18] or if they wished to receive hematopoietic stem-cell transplantation. A requirement for therapeutic intervention was not well defined and, consequently, some of the patients enrolled were treated immediately after diagnosis without watchful waiting.

All patients gave written, informed consent before enrollment. All case report forms were collected, managed, and analyzed at the Japan Clinical Oncology Group [JCOG] Data Center. The report was monitored (without any comparative data between the two arms) through a semiannual review by the JCOG Data and Safety Monitoring Committee. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review boards at all study sites.

Study Treatment

CHOP consisted of 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, and 1.4 mg/m² vincristine (capped at 2.0 mg) taken intravenously on day 1 and 100 mg oral prednisone taken daily on days 1 to 5. CHOP cycles were repeated every 3 weeks (arm A) or every 2 weeks (arm B) for a total of six cycles. In both arms, rituximab was given 2 days before CHOP cycles 1, 2, 4, and 6, for a total of four doses, following R-CHOP dosage in the preceding study.[4] In the R-CHOP-14 arm, G-CSF was administered daily for a period of 6 days, starting on day 8 and ending 2 days before CHOP of the subsequent cycle.
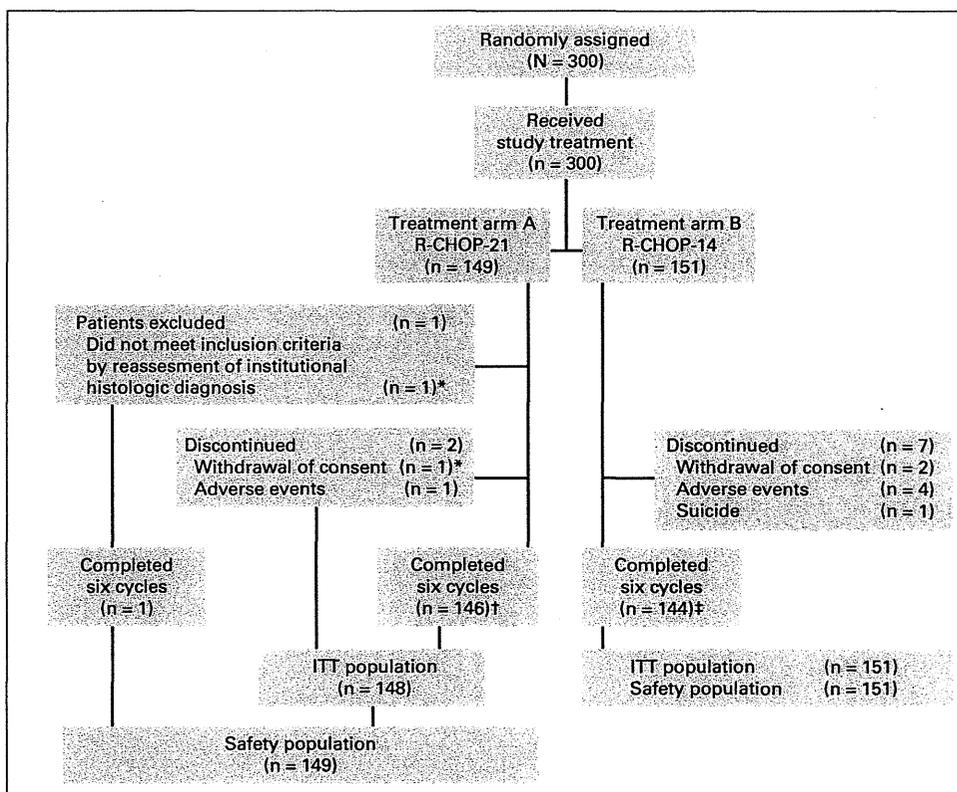
Fig 1. CONSORT diagram showing the flow of patient enrollment and disposition throughout the trial. ITT, intent to treat; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks. (*) Patients enrolled onto the phase II trial. (†) Thirty-five and (‡) 36 patients were enrolled onto the phase II trial for R-CHOP-21 and R-CHOP-14, respectively.

In the R-CHOP-21 arm, G-CSF was administered according to the American Society of Clinical Oncology guidelines.[19] Maintenance use of rituximab was not allowed.

After 74 patients had been enrolled onto this study, the Japanese National Health Insurance policy regarding rituximab treatment changed. In October 2003, the protocol was revised so that rituximab could be given in every CHOP cycle for a total of six doses. Consequently, of the 291 patients who completed the protocol treatment, 76 patients received four doses of rituximab, three patients received five doses, and 212 patients (71% of the total) received six doses. During the accrual period, seven of 134 of the patients treated with R-CHOP-21 developed interstitial pneumonitis, which was caused by *Pneumocystis jiroveci* in six of these patients. The original protocol stipulated prophylaxis only for the patients treated with R-CHOP-14; the protocol was thus amended to include both arms. To prevent HBV reactivation, we revised the protocol in March 2006 to allow the prescription of anti-HBV medication to patients in both treatment arms with a high titer of antibodies against the HBV core antigen.[20-22]

Assessments

Tumor assessments were performed on all target lesions identified at baseline by CT scans after three R-CHOP cycles and at different times after completion of six-cycle R-CHOP (ie, around the eighth week, every 6 months for the first 2 years, and annually thereafter). Tumor response was assessed by using the International Workshop Criteria.[23] CT films from patients who achieved a complete response (CR) or an unconfirmed CR (CRu) during phase II were evaluated by an independent CT review board consisting of two

Table 1. Baseline Patient Characteristics

Characteristic	R-CHOP-21 (n = 149)				R-CHOP-14 (n = 151)				Total (N = 300)				P*
	No. of Patients	No. of Patients With FL	%	Percent of Patients With FL	No. of Patients	No. of Patients With FL	%	Percent of Patients With FL	No. of Patients	No. of Patients With FL	%	Percent of Patients With FL	
Age, years†													
Median	54				55				54.5				.93
Range	27 to 69				33 to 69				27 to 69				
≥ 61	37		25		38		25		75		25		1.00
Male sex	70		47		73		48		143		48		.82
Bulky disease†‡	32		21		31		21		63		21		.89
Elevated LDH	28		19		30		20		58		19		.88
Stage IV	99		66		99		66		198		66		.90
B symptoms	17		11		11		7		28		9		.24
ECOG PS 1 or 2	26		17		31		21		57		19		.56
More than one extranodal site	18		12		31		21		49		16		.06
Hemoglobin < 12 g/dL	25		17		39		26		64		21		.07
At least five affected nodal areas	55		37		51		34		106		35		.63
FLIPI risk group													
Low	52	45	35	34	45	42	30	32	97	87	32	33	
Intermediate	61	56	41	42	64	59	42	45	125	115	42	43	.60
High	36	32	24	24	42	31	28	23	78	63	26	24	
IPI risk group													
Low	82		55		73		48		155		52		
Low-intermediate	50		34		56		37		106		35		.70
High-intermediate	16		11		21		14		37		12		
High	1		1		1		1		2		1		
Histology (central review)													
FL (grades 1, 2, and 3A)	125		84		123		81		248		83		
FL (grade 3B)	8		5		9		6		17		6		
MZL	0		0		6		4		6		2		
SLL	1		1		1		1		2		1		
Other indolent B-cell NHLs	8		5		5		3		13		4		.28
MCL§	2		1		2		1		4		1		
DLBCL§	4		3		2		1		6		2		
Plasmacytoma§	0		0		1		1		1		0.3		
Others§	1		1		2		1		3		1		

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma (FL grade 3B includes follicular large plus diffuse large); FLIPI, Follicular Lymphoma International Prognostic Index; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin's lymphoma; PS, performance status; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks; SLL, small lymphocytic lymphoma.
*Wilcoxon rank sum test.
†Dynamic allocation adjustment factors in randomization.
‡Bulky disease was defined as a nodal or extranodal mass of ≥10 cm horizontal diameter on a computed tomography scan.
§Patients judged ineligible by the central pathologic review.

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radiologists (T.N. and T.T.) and one oncologist (T.W.). Histopathologic specimens from all 300 patients were reviewed by three hematopathologists (K.T., Y. Matsuno, MD, and Tadashi Yoshino, MD), as previously described.[24] Toxicity was assessed on the basis of the National Cancer Institute Common Toxicity Criteria Version 2.0.

Study End Points and Statistical Analyses

The primary end points of phase II and the whole phase III study were CR/CRu rate and progression-free survival (PFS), respectively; the secondary end points of phase II were overall response rate and toxicities and those of phase III were overall survival (OS) and toxicities. PFS was calculated from the date of random assignment to the date of relapse, progression, or death from any cause, and it was censored at the last verifiable progression-free date. OS was calculated from the date of random assignment to the date of death from any cause and censored at the last follow-up. PFS and OS were estimated by using the Kaplan-Meier method, and curves were compared (significance level of one-sided $\alpha = .05$) by using a log-rank test stratified by bulky disease and age (≥ 61 or ≤ 60 years). Hazard ratios (HRs) of treatment effects were estimated through the stratified Cox regression model with bulky disease and age as the strata. PFS and OS were subsequently analyzed by using the Cox regression model exploratorily to assess the effects of treatment with the prognostic factors, including the components of the Follicular Lymphoma International Prognostic Index (FLIPI)[25] or the International Prognostic Index (IPI),[26] bulky disease, and sex.

The planned sample size was 200 patients to detect a prolongation of 3-year PFS in the R-CHOP-14 arm from 50% with R-CHOP-21 to 65% with an 80% power and a one-sided $\alpha = .05$. The planned study period was 4 years for accrual and an additional 3 years for follow-up. Two interim analyses were planned. The first interim analysis was conducted during phase II to test whether the CR/CRu rate for each arm was superior to the predefined threshold (35%) with a one-sided $\alpha = .15$ and $\beta = .10$ to detect a 20% increase. The threshold data were based on the results of the standard CHOP regimen without rituximab.[27] The second interim analysis was conducted when all of the patients had registered in phase III to assess necessity of further follow-up; this analysis compared the arms that used the O'Brien and Fleming stopping boundaries by using the Lan and DeMets α-spending function to control the type I error for the primary end point. Throughout the study period, the researchers were blind to the primary end point interim analysis results. The sample size was re-evaluated independently from the interim analysis results when the accrual rate was higher than expected, and the protocol was subsequently revised. To maintain the required statistical power and to detect a 12% increase in the 3-year PFS of patients treated with R-CHOP-14, the sample size was increased to 300 patients (expected number of events, 181) over 4.5 years, using the same initial follow-up plan for these patients. All statistical analyses were performed by using SAS software, release 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 300 patients were enrolled from 44 institutions between September 2002 and February 2007 (Fig 1). The median age of the patients was 54.5 years. The patient characteristics were well balanced between arms except for B symptoms, hemoglobin levels, the number of extranodal sites, and the FLIPI risk group (Table 1). The doses delivered were the same between arms, except for vincristine (Appendix Fig A1, online only).

Response Rate

At the first interim analysis, the CR/CRu rates of the 73 patients enrolled in phase II of the R-CHOP-21 and R-CHOP-14 arms were 49% (17 CRs plus one CRu in 37 patients) and 50% (13 CRs plus five CRus in 36 patients), respectively, according to the central CT review.

Since one patient was excluded because of histologic transformation by institutional diagnosis, 299 patients were eligible for the survival analysis (Fig 1). The CR/CRu rates obtained from the case report forms for the 299 patients of the entire phase III study were 78% (68 CRs plus 48 CRu's in 148 patients) and 76% (76 CRs plus 39 CRus in 151 patients), respectively. The overall response rate was 97% for each arm. According to the FLIPI, CRs and CRus were achieved in 24 and 18 (93% in total) of the 45 patients with low-risk FL undergoing R-CHOP-21, respectively, and 29 and eight (88%) of the 42 patients with low-risk FL undergoing R-CHOP-14, respectively. For the patients with intermediate-risk FL, 82% of 56 patients (26 CRs and 20 CRus) undergoing R-CHOP-21 and 80% of 59 patients (26 CRs and 21 CRus) undergoing R-CHOP-14 achieved a CR or CRu. For the patients with high-risk FL, 15 and seven (69%) of 32 patients undergoing R-CHOP-21 and 14 and six (65%) of 31 patients undergoing R-CHOP-14 achieved a CR or CRu, respectively.
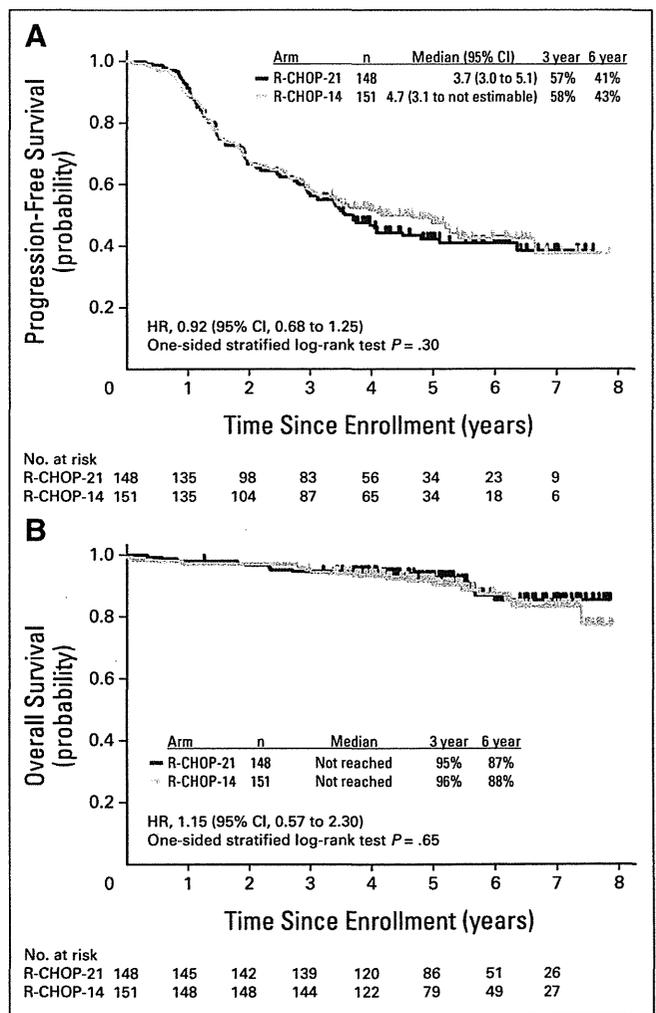
Fig 2. (A) Progression-free survival and (B) overall survival by treatment for patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma. The median follow-up time was 5.2 years. HR, hazard ratio; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks.

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PFS and OS

In the primary analysis for PFS in the eligible population at 4.7 years (median follow-up time), there was no significant difference between the arms (one-sided $P = .35$ with stratified log-rank test; multiplicity-adjusted one-sided significance level $= 0.045$; HR, 0.94; 95% CI, 0.69 to 1.28). At 5.2 years (the median follow-up time), 82 (R-CHOP-21) and 78 (R-CHOP-14) patients had a documented progression, and two patients from each treatment died before progres-

sion. Although we used a post hoc power calculation, we expected at least 80% power, as designed, to detect a difference between the arms with these events. The median PFS times were 3.7 and 4.7 years for R-CHOP-21 and R-CHOP-14, respectively, and the 3-year PFS (R-CHOP-21: 57%; R-CHOP-14: 58%) and 6-year PFS (R-CHOP-21: 41%; R-CHOP-14: 43%) were almost identical (HR, 0.92; 95% CI, 0.68 to 1.25; $P = .30$; Fig 2A). There was no significant difference between arms in OS (HR, 1.15; 95% CI, 0.57 to 2.30; $P = .65$; Fig 2B).
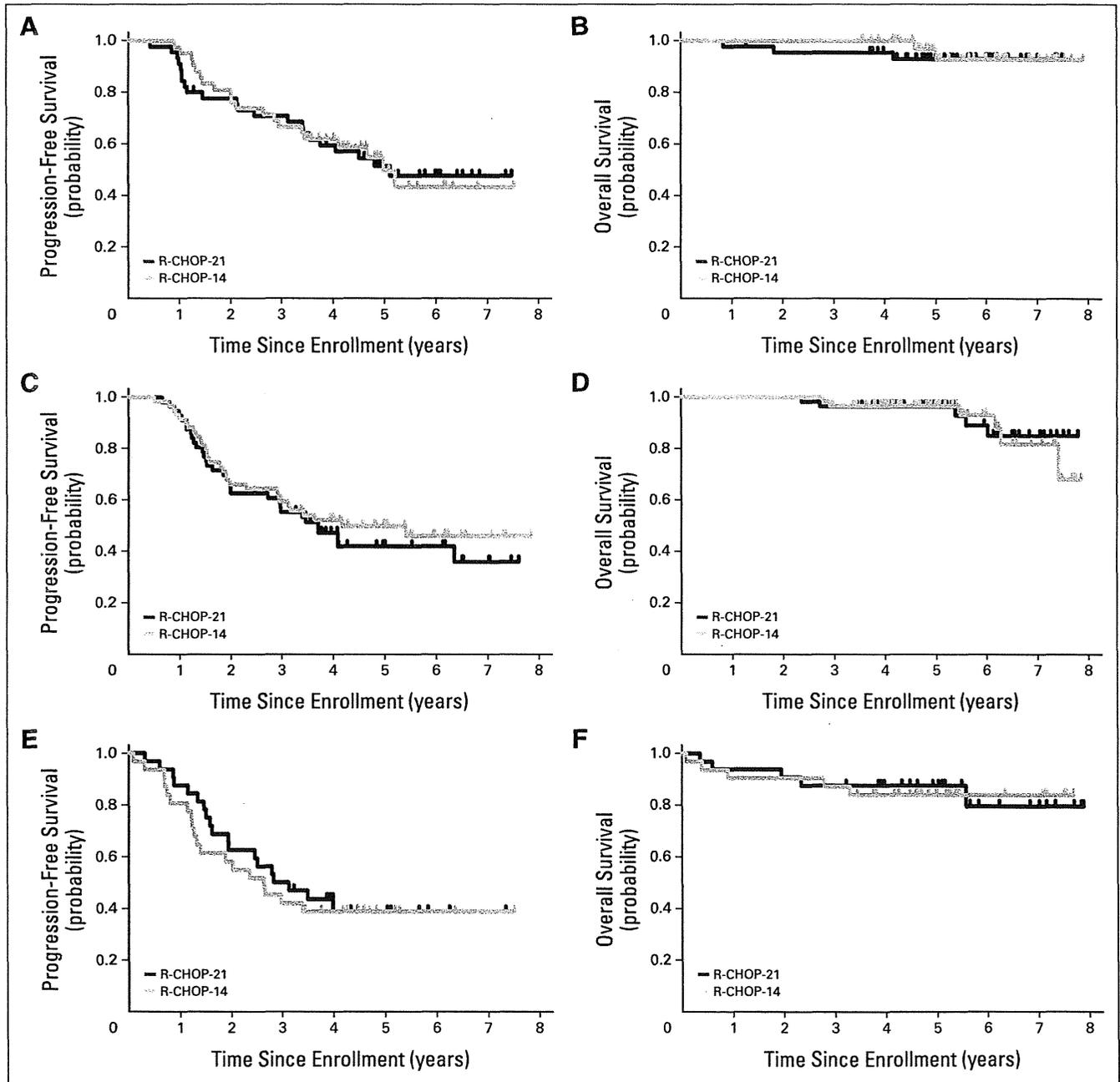
Fig 3. Progression-free survival (A, C, E) and overall survival (B, D, F) by treatment for patients in the low-risk (n = 87; A, B), intermediate-risk (n = 115; C, D), and high-risk (n = 63; E, F) groups according to the Follicular Lymphoma International Prognostic Index for the 265 patients with follicular lymphoma who were eligible for survival analysis. R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks.

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A

Progression-Free Survival

Subgroup	N (A/B)	HR and 95% CI	HR (95% CI)
IPI			
Low or low-intermediate	131/129		0.86 (0.61 to 1.20)
High-intermediate or high	17/22		1.22 (0.56 to 2.62)
FLIPI			
Low	52/45		0.81 (0.46 to 1.42)
Intermediate	61/64		0.85 (0.53 to 1.37)
High	35/42		1.19 (0.67 to 2.12)
Age, years			
≤ 60	111/113		0.96 (0.67 to 1.36)
≥ 61	37/38		0.82 (0.44 to 1.53)
Sex			
Female	78/78		0.84 (0.53 to 1.34)
Male	70/73		0.99 (0.66 to 1.50)
Bulky mass			
No	116/120		0.80 (0.57 to 1.14)
Yes	32/31		1.48 (0.78 to 2.79)
Serum LDH level			
≤ ULN	121/121		0.85 (0.60 to 1.20)
> ULN	27/30		1.35 (0.69 to 2.62)
Ann Arbor stage			
III	50/52		0.55 (0.31 to 0.97)
IV	98/99		1.17 (0.81 to 1.69)
Performance status			
0	123/120		0.99 (0.70 to 1.39)
1 or 2	25/31		0.68 (0.34 to 1.35)
Extranodal involvement			
0 or 1	130/120		0.83 (0.59 to 1.17)
2 or more	18/31		1.36 (0.63 to 2.91)
Hemoglobin level, g/dL			
≥ 12	124/112		1.05 (0.74 to 1.48)
< 12	24/39		0.60 (0.31 to 1.17)
No. of nodal sites			
0-4	93/100		0.74 (0.49 to 1.10)
5 or more	55/51		1.36 (0.84 to 2.20)
Overall	148/151		0.92 (0.68 to 1.25)

0.1   1   10

Favors R-CHOP-14   Favors R-CHOP-21

B

Overall Survival

Subgroup	N (A/B)	HR and 95% CI	HR (95% CI)
IPI			
Low or low-intermediate	131/129		1.48 (0.63 to 3.47)
High-intermediate or high	17/22		0.47 (0.13 to 1.65)
FLIPI			
Low	52/45		0.57 (0.10 to 3.11)
Intermediate	61/64		0.96 (0.31 to 2.99)
High	35/42		1.54 (0.51 to 4.58)
Age, years			
≤ 60	111/113		1.32 (0.56 to 3.14)
≥ 61	37/38		0.81 (0.25 to 2.65)
Sex			
Female	78/78		0.79 (0.24 to 2.61)
Male	70/73		1.29 (0.54 to 3.07)
Bulky mass			
No	116/120		0.99 (0.43 to 2.29)
Yes	32/31		1.51 (0.43 to 5.36)
Serum LDH level			
≤ ULN	121/121		0.81 (0.32 to 2.05)
> ULN	27/30		1.59 (0.53 to 4.75)
Ann Arbor stage			
III	50/52		0.80 (0.24 to 2.63)
IV	98/99		1.34 (0.56 to 3.17)
Performance status			
0	123/120		1.36 (0.60 to 3.10)
1 or 2	25/31		0.62 (0.17 to 2.33)
Extranodal involvement			
0 or 1	130/120		1.24 (0.55 to 2.76)
2 or more	18/31		0.78 (0.19 to 3.15)
Hemoglobin level, g/dL			
≥ 12	124/112		1.32 (0.63 to 2.79)
< 12	24/39		0.58 (0.08 to 4.15)
No. of nodal sites			
0-4	93/100		0.59 (0.23 to 1.56)
5 or more	55/51		2.43 (0.83 to 7.15)
Overall	148/151		1.15 (0.57 to 2.30)

0.1   1   10

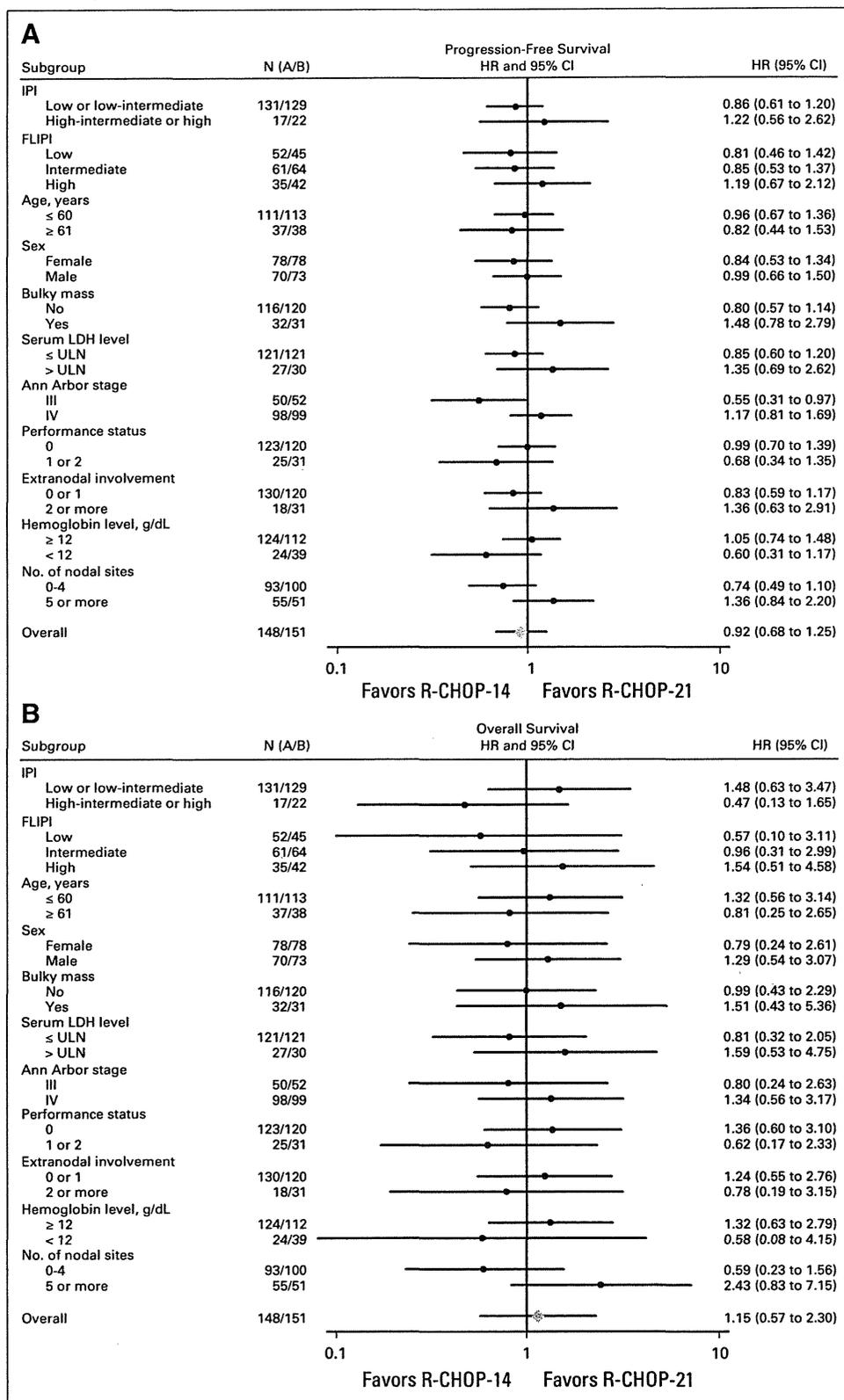Favors R-CHOP-14   Favors R-CHOP-21

Fig 4. Forest plots of hazard ratios (HRs), comparing (A) progression-free survival and (B) overall survival among patients with previously untreated, advanced-stage indolent B-cell non-Hodgkin's lymphoma assigned to immunochemotherapy with either R-CHOP-14 (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] administered every 2 weeks with granulocyte colony-stimulating factor) or R-CHOP-21 (R-CHOP administered every 3 weeks), according to the risk subgroups classified by the International Prognostic Index (IPI), the Follicular Lymphoma International Prognostic Index (FLIPI), or age. Closed circles represent the hazard ratios, and the horizontal bars represent the 95% CIs. LDH, lactate dehydrogenase; ULN, upper limit of normal.

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The median PFS results for the 286 histopathologically eligible patients were similar (R-CHOP-21: 3.7 years; R-CHOP-14: 4.2 years). The exploratory subgroup analysis of the 34 patients with grade 3 FL indicated no significant difference in PFS (R-CHOP-21: 3.5 years; R-CHOP-14: not estimable; HR, 0.73; 95% CI, 0.27 to 1.94; P = .26).

Twenty patients (7% of all patients; 10 from each treatment) died as a result of progressive disease. Six patients (2%; three from each treatment) died as a result of other diseases; three patients treated with R-CHOP-21 died as a result of acute myeloid leukemia, subarachnoid hemorrhage, or pneumonia during glucocorticoid treatment for pemphigus vulgaris, and three patients treated with R-CHOP-14 died as a result of colon cancer, acute lymphoblastic leukemia, or cerebral hemorrhage. Five patients (2%; two, R-CHOP-21; three, R-CHOP-14) died as a result of treatment-related events after salvage therapies, including four relevant to allogenic stem-cell transplantation and one liver cirrhosis associated with HBV reactivation after rituximab-alone treatment for relapse (R-CHOP-21). One suicide (R-CHOP-14) occurred during the protocol treatment.

According to the FLIPI, the 6-year PFS of patients with FL treated with R-CHOP-21 or R-CHOP-14 were 48% and 43% in the low-risk group, 42% and 46% in the intermediate-risk group, and 39% each in the high-risk group (Figs 3A, 3C, and 3E). The 6-year OS of patients with FL treated with R-CHOP-21 or R-CHOP-14 were 93% each in the low-risk group, 89% and 93% in the intermediate-risk group, and 80% and 84% in the high-risk group, respectively (Figs 3B, 3D, and 3F). There were no differences found for any of the three risk groups in the 6-year PFS or OS. Moreover, the two treatments did not differ with respect to PFS or OS according to the IPI risk categories (low or low-intermediate versus high-intermediate or high) or on the basis of patient age ($\leq$ 60 $v \geq$ 61 years; Fig 4).

A Cox proportional hazard regression analysis was used to assess the effects of various parameters on the primary analysis. These factors did not affect the point estimate of the treatment arms (Fig 4). Only male sex was a significantly unfavorable PFS parameter (Table 2).

Male sex and increased lactate dehydrogenase were unfavorable predictors of OS (Appendix Table A1, online only).

Toxicity

We compared adverse events between treatments for all 300 patients who underwent the protocol treatment (Table 3). Grade 4 neutropenia and grade 3 infection were encountered more frequently during treatment with R-CHOP-21 than during treatment with R-CHOP-14 (35 of 149 [23%] v 18 of 151 [12%], respectively). Nevertheless, no patient experienced grade 4 infection following either treatment. More patients experienced a grade 3 to 4 hemoglobin decrease with R-CHOP-14; however, more patients in the R-CHOP-14 arm were diagnosed with anemia before treatment (Table 1). Furthermore, patients assigned to R-CHOP-14 experienced grade 3 peripheral neuropathy more frequently than did patients with R-CHOP-21 (three of 149 [2%] v 11 of 151 [7%],

Table 2. Clinicopathologic Parameters Influencing the PFS of Previously Untreated, Advanced, Indolent B-Cell NHL in a Multivariate Analysis

Parameter	HR*	95% CI	P
Treatment arm, R-CHOP-21 v R-CHOP-14	0.93	0.68 to 1.27	.64
Age (years), $\leq$ 60 $v \geq$ 61	1.00	0.70 to 1.43	.99
Sex, female v male	1.65	1.18 to 2.30	< .01
Bulky disease, < 10 cm $v \geq$ 10 cm	1.03	0.68 to 1.54	.91
LDH, $\leq$ ULN v > ULN	1.36	0.90 to 2.07	.15
Stage, III v IV	1.20	0.84 to 1.72	.32
ECOG PS, 0 v 1 or 2	1.13	0.76 to 1.68	.54
No. of extranodal sites, 0 or 1 $v \geq$ 2	1.20	0.79 to 1.83	.39
Hemoglobin, $\geq$ 12 g/dL v < 12 g/dL	1.15	0.77 to 1.74	.49
No. of affected nodal areas, $\leq$ 4 $v \geq$ 5	1.25	0.89 to 1.76	.20

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; NHL, non-Hodgkin's lymphoma; PFS, progression-free survival; PS, performance status; R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks; UNL, upper limit of normal.
*HRs are presented as the risk of the right-side category (ie, right side of v in Parameter column) to the left-side category (ie, left side of v).

Table 3. Comparison of Grade 3 or 4 Adverse Events* Between the R-CHOP-21 and R-CHOP-14 Treatment Arms

Adverse Events	Grade	Arm A (R-CHOP-21) (n = 149) No.	%	Arm B (R-CHOP-14) (n = 151) No.	%
Hematologic					
Neutropenia	3 or 4	144	97	102	68
Neutropenia	4	126	85	56	37
Hemoglobin	3 or 4	3	2	24	16
Thrombocytopenia†	3	2	1	4	3
Nonhematologic					
AST	3	4	3	4	3
ALT	3	7	5	8	5
Hyperglycemia	3	8	6	7	5
Hypocalcemia‡	4	0	0	1	1
Hyponatremia	3	4	3	4	3
Hypokalemia	3	2	1	1	1
Supraventricular arrhythmia	3	1	1	0	0
Fever	3	0	0	2	1
Appetite loss	3	6	4	11	7
Constipation	3	6	4	10	7
Diarrhea	3	1	1	2	1
Ileus	3	2	1	5	3
Nausea	3	7	5	8	5
Stomatitis/pharyngitis	3	2	1	0	0
Vomiting	3	4	3	3	2
Hematuria	3	1	1	1	1
Febrile neutropenia§	3	22	15	10	7
Infection with grade 3 neutropenia§	3	21	14	8	5
Infection without neutropenia§	3	7	5	5	3
Peripheral neuropathy	3	3	2	11	7
Dyspnea (shortness of breath)	3	4	3	0	0
Interstitial pneumonitis	3	5	3	0	0

Abbreviations: R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks.
*Adverse events were evaluated by the worst grades throughout all of the cycles per patient, according to the National Cancer Institute-Common Toxicity Criteria, Version 2.0.
†No grade 4 thrombocytopenia was observed.
‡Except for hypocalcemia, no grade 4 nonhematologic toxicities were observed.
§Grade 3 infection. The number of patients who experienced any of these three was 35 (23%) in arm A and 18 (12%) in arm B.

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respectively). Grade 3 appetite loss, constipation, and ileus followed the same trend. Three hematologic malignancies were found in total: in the R-CHOP-21 arm, myelodysplasia (patient remains alive) and acute myeloid leukemia were diagnosed in one patient each, and in the R-CHOP-14 arm, one patient was diagnosed with acute lymphoblastic leukemia.

DISCUSSION

The results from this phase II/III study demonstrate that R-CHOP-14 is not superior to R-CHOP-21 in terms of PFS, although R-CHOP is highly effective as an initial treatment for indolent B-cell NHL, regardless of the administration schedule, as determined by a long-term follow-up. The median follow-up time for all randomly assigned patients was 5.2 years at the planned analysis time point 3 years after the last patient enrollment. Therefore, our mature analysis results have not been reported from other RCTs that use rituximab to treat FL.[1,2] However, our attempt to improve PFS by using a dose-dense strategy with the immunomodulatory agent G-CSF failed.

The 3-year PFS for patients treated with R-CHOP-21 in this study matched that for the control patients in the Primary RItuximab and MAintenance (PRIMA) study (58%).[28] The lower CR/CRu rates in the first interim analysis (compared with the entire phase III population) could be due to two reasons: First, the central CT review was used to judge the transition to phase III. Second, the majority of patients enrolled in phase II received four doses of rituximab.

Our subset analysis (according to the FLIPI) demonstrates that there are no differences in PFS or OS between treatments for any of the three risk groups. The proportion of high-risk patients in our study was smaller than that in the German Low-Grade Lymphoma Study Group (GLSG)[29] (24% v 45%). The difference in the proportions of high-risk patients between the two studies was partly due to different inclusion criteria.

Grade 4 neutropenia and grade 3 infection occurred more often during R-CHOP-21 than during R-CHOP-14. However, no grade 4 infections were observed in either arm, although a total of 59 patients (40%) received G-CSF (13 in one cycle, nine each in two and three cycles, six in four cycles, 10 in five cycles, and 12 in six cycles) with R-CHOP-21.[1] Seven patients (4.7% of patients treated with R-CHOP-21) developed interstitial pneumonitis, and six of these cases were caused by Pneumocystis jiroveci. No cases of interstitial pneumonitis were observed in the patients treated with R-CHOP-14 because they were prescribed prophylactic treatment early in the study period. In our previous study, CHOP-14 treatment was frequently complicated by Pneumocystis carinii pneumonitis.[11] Alveolar damage caused by rituximab-induced cytokine production and lymphopenia might have partially contributed to the development of Pneumocystis carinii pneumonitis.[30,31] Furthermore, as a result of prophylaxis, there were no reports of hepatitis caused by HBV reactivation during the trial treatment, except for one patient who died as a result of liver cirrhosis associated with HBV reactivation following salvage treatment with rituximab.

Three and five secondary malignancies were found following R-CHOP-21 and R-CHOP-14, respectively. The incidence of secondary hematologic malignancies for the combined treatments was 1% at the time of analysis.

Potentially efficacious treatment options that will further improve the PFS of patients with untreated advanced indolent B-cell NHL include consolidative radioimmunotherapy[32] and/or rituximab maintenance.[28] Another potential efficacious first-line treatment is R-bendamustine.[33]

In summary, to the best of our knowledge, the JCOG 0203 study provides the first phase III data illustrating that a dose-dense strategy using the immunomodulatory agent G-CSF does not prolong PFS in previously untreated indolent B-cell NHL and that R-CHOP-21 is still one of the standard treatments for this population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

AUTHOR CONTRIBUTIONS

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資　料

がん診療の経済的な負担に関するアンケート調査

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「がんの医療経済的な解析を踏まえた患者負担の在り方に関する研究」

研究代表者 ： 濃沼　信夫　（東北大学教授）
研究分担者 ： 石岡　千加史（東北大学教授）
研究協力者 ： 東北大学病院　化学療法センター運用ワーキンググループ

＜調査の趣旨＞

　このアンケートは、経済的な負担ができるだけ少ない、がん医療の実践に向けた基礎資料を得ることを目的としています。

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事務局

〒980-8575　仙台市青葉区星陵町 2-1
東北大学大学院　医学系研究科　医療管理学分野
伊藤道哉、金子さゆり、伊藤てる子
TEL：022-717-8128
FAX：022-717-8130

がん診療の経済的な負担に関するアンケート調査

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