improvement in pancreatic pain and worsening in body image, changes in bowel habits, treatment-related side-effects, and ability to plan for the future (data not shown). Patients on placebo reported a 5-point or more mean change from baseline in emotional functioning, pain, constipation, insomnia, and loss of appetite (all improved) on the QLQ-C30; similar changes were seen in pancreatic pain, fear of future health, and cachexia (all improved) on the QLQ-PAN26 (data not shown).

Discussion

This randomised phase 3 trial clearly shows that the addition of axitinib to gemcitabine does not improve survival in patients with locally advanced or metastatic pancreatic cancer. These data also confirm the findings obtained in previous phase 3 studies of the VEGF inhibitors bevacizumab and aflibercept that inhibition of this pathway is ineffective in patients with this disease (panel).[13–15]

In view of the long history of promising phase 2 single-group trials that have yielded negative phase 3 results, some investigators have concluded that a randomised phase 2 trial is the optimum method to predict the benefit of a novel agent in the phase 3 setting.[16] The randomised phase 2 trial design reduces the bias of a comparison with historical data, as well as the patient selection bias. As our study shows, the results of hypothesis-generating, exploratory, randomised, phase 2 studies are not always replicated in randomised phase 3 trials. Indeed, the results of this trial underscore the importance of implementation of phase 3 testing only after a robust signal from appropriately designed phase 2 trials.[17]

The decision to evaluate axitinib in a phase 3 study was based on the results of a fairly small (103 patients), exploratory, randomised, phase 2 study in which gemcitabine plus axitinib showed a non-significant improvement in median overall survival compared with gemcitabine (6·9 months, 95% CI 5·3–10·1 *vs* 5·6 months, 3·9–8·8; HR 0·71, 95% CI 0·44–1·13).[6] That phase 2 study was neither intended nor powered to show a significant difference between the two groups, and the confidence intervals for median overall survival overlapped. Additionally, the confidence interval for the HR contained 1·0. When the decision was made to move forward into phase 3, the HR for overall survival in the phase 2 study was 0·74 in favour of the axitinib plus gemcitabine group. Statistical modelling that took this treatment effect into account, as well as its variability, determined that there was a roughly 65% chance that the phase 3 study would have positive results. We regarded this finding as sufficient justification to undertake this phase 3 trial, although we recognised the significant risk in moving forward from a small phase 2 study to a large phase 3 trial.

The treatment effect in the randomised phase 2 trial was greatest in patients with locally advanced disease and in those with ECOG performance statuses of 0 and 1. The inclusion of 25% of patients with locally advanced disease and almost 50% of patients with performance status 0, plus the exclusion of patients with any thrombosis requiring anticoagulation (who tend to have reduced survival rates), clearly account for the longer-than-anticipated median survival of more than 8 months that was recorded in the control group of this trial. A retrospective analysis from a phase 3 study of gemcitabine and erlotinib plus either bevacizumab or placebo suggests that clinical outcomes might correlate with a genetic locus in the tyrosine kinase domain of VEGF receptor 1.[18] Pharmacogenetic analyses are underway for the present study.

The addition of axitinib to gemcitabine resulted in acceptable tolerability, with a similar incidence of grade 3 or higher adverse events in both groups. Only grade 3 or higher asthenia and hypertension occurred more frequently in patients receiving axitinib than in those allocated placebo. Hypertension was manageable with antihypertensive drugs or axitinib dose reductions, or both. Although venous thrombosis, gastrointestinal bleeding, and gastrointestinal perforations have often been reported with VEGF inhibitors, these were not increased in the axitinib group of this trial.

Analysis of health-related quality of life showed improvements in pancreatic cancer symptoms of pain in both treatment groups. In the axitinib plus gemcitabine group, minor worsening was reported in diarrhoea, fatigue, and changes in bowel habits—side-effects that are typically associated with VEGF inhibition.

Despite the 42% incidence of increased TSH concentration (≥5 μU/mL) in the axitinib plus gemcitabine group, only 6% of patients were diagnosed with hypothyroidism and received hormone replacement therapy. Whether any patients with TSH increase had subclinical hypothyroidism,

Panel: Research in context

Systematic review

Although a systematic review was not done as part of the planning for this trial, the existing evidence in this area was identified by literature (Medline) searches. Medline search terms included "pancreatic cancer", "chemotherapy", "gemcitabine"; search limited to English language, 1997–2007. Previous key trials of gemcitabine-based regimens in pancreatic adenocarcinoma have shown poor outcomes and low survival rates. An exploratory randomised phase 2 trial[6] showed that the combination of gemcitabine and axitinib in this setting resulted in a numerical improvement in median overall survival compared with gemcitabine alone. The rationale for the present phase 3 trial of axitinib plus gemcitabine was to further investigate and to confirm findings from the phase 2 study.

Interpretation

Results from this trial show that the addition of axitinib to gemcitabine does not improve survival for patients with advanced pancreatic cancer. The data thus add to increasing evidence that targeting of vascular endothelial growth factor (VEGF) signalling is an ineffective strategy in advanced pancreatic cancer. This conclusion is supported by results of phase 3 trials showing that addition of other VEGF inhibitors such as bevacizumab or aflibercept to gemcitabine did not improve survival compared with gemcitabine plus placebo in patients with advanced pancreatic cancer. On the basis of data from this trial, we recommend that no changes to treatment paradigms for advanced pancreatic cancer are indicated.

or whether hormone replacement therapy would have been beneficial, is uncertain.

In conclusion, the addition of axitinib to gemcitabine does not improve survival for patients with advanced pancreatic cancer. These results add to increasing evidence that targeting of VEGF signalling is an ineffective strategy in this disease.

Contributors

HLK contributed to study design, data collection, analysis, and interpretation, literature search, and writing of the report. TI contributed to data collection and interpretation and review of the report. DJR contributed to patient inclusion, data interpretation, and writing and review of the report. JB contributed to inclusion of patients in the study and writing of the report. RL contributed to recruitment and follow-up of patients and review of the report. TO contributed to recruitment and management of patients, data collection, and review of the report. AF contributed to data collection and interpretation and review of the report. JF contributed to study design, data collection and interpretation, and review of the report. YSP contributed to data collection and interpretation and writing and review of the report. SO contributed to data collection and interpretation and review of the report. GMS contributed to data collection and writing of the report. HSW provided study design advice and contributed to recruitment of study participants, UK ethics submission, and report review and contribution. PCT contributed to study design, data analysis and interpretation, and writing of the report. PB contributed to study design, data collection and analysis, data interpretation, and writing of the report. ADR contributed to study design, data collection, analysis, and interpretation, and writing of the report. SK contributed to design, writing of the protocol, data analysis and interpretation, and editing of the report. EVC contributed to data collection, analysis, and interpretation and writing of the report. All authors provided final approval of the report.

Conflicts of interest

Pfizer provided TI with a flight ticket and accommodation for attending an investigator meeting for the reported study (the meeting was sponsored by Pfizer); Pfizer paid TI's institution the necessary cost to conduct the study. JB has received compensation for board membership from Roche, Bayer, and Boehringer; and payment for lectures, including service on speakers' bureaus from Roche and AstraZeneca. RL's institution received a fee per patient from Pfizer for participation in the study (research nurse work, etc). TO's institution has received research funding from Pfizer in relation to the work under consideration for publication; it has also received research funding unrelated to the submitted work from Eli Lilly, Taiho, Dainippon-Sumitomo, Bayer, Chugai, Otsuka, Novartis, Kowa, Pfizer, Yakult, Eisai, Oncotherapy Science, Bristol-Myers Squibb, Abbott, Takeda Bio, and Nippon Kayaku. TO received travel expenses for the study from Pfizer; he has also received payment for lectures unrelated to the submitted work from Taiho, Eli Lilly, Asuka, Bayer, Chugai, Novartis, Torii, Nippon Kayaku, Pfizer, Janssen, AstraZeneca, Dainippon-Sumitomo, Wyeth, and Ajinomoto. Pfizer provided AF with a flight ticket and accommodation for attending an investigator meeting for the reported study (the meeting was sponsored by Pfizer); Pfizer paid AF's institution the necessary cost to conduct the study. JF has received payment for lectures, including service on speakers' bureaus from Bayer, Taiho, Eli Lilly, and Eisai; Pfizer paid JF's institution the necessary cost to conduct the study. Pfizer paid SO's institution the necessary cost to conduct the study; SO's institution has received research funding from Eli Lilly, Taiho, Chugai, Yakult, Oncotherapy Science, Abbott, and Dainippon-Sumitomo. SO has received payment for lectures from Eli Lilly, Taiho, Kyowa Hakko Kirin, and Hisamitsu. GMS's institution has received a grant from Pfizer in relation to the work under consideration for publication. HSW's institution received money from Pfizer for running the trial and per patient payments to cover trial costs; HSW has received compensation from Pfizer for participation in two advisory boards during the past year (clinical trial and scientific development programmes by Pfizer). EVC's institution received a grant from Pfizer in relation to the work under consideration for publication; and it also has grants or grants pending from Pfizer outside of the submitted work. PCT, PB, ADR, and SK are compensated as employees of Pfizer and own stock or stock options in Pfizer. HLK, DJR, and YSP declare that they have no conflicts of interest.

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original article

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Phase III trial of CHOP-21 versus CHOP-14 for aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG 9809

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Background: CHOP-21 has remained the standard chemotherapy for aggressive non-Hodgkin's lymphoma (NHL), and dose intensification is a potential strategy for improving therapeutic results. We conducted a phase III trial to determine whether dose-dense strategy involving interval shortening of CHOP (CHOP-14) is superior to CHOP-21.

Patients and methods: A total of 323 previously untreated patients (aged 15–69 years) with stages II–IV aggressive NHL were randomized. The primary end point was progression-free survival (PFS).

Results: Treatment compliance was comparable in both study arms. At 7-year follow-up, no substantial differences were observed in PFS and overall survival (OS) between CHOP-21 (n = 161) and CHOP-14 (n = 162) arms. Median PFS was 2.8 and 2.6 years with CHOP-21 and CHOP-14, respectively (one-sided log-rank P = 0.79). Eight-year OS and PFS rates were 56% and 42% [95% confidence interval (CI) 47% to 64% and 34% to 49%], respectively, with CHOP-21 and 55% and 38% (95% CI 47% to 63% and 31% to 46%), respectively, with CHOP-14. Subgroup analyses showed no remarkable differences in PFS or OS for patients stratified as per the International Prognostic Index or by age.

Conclusion: Dose-intensification strategy involving interval shortening of CHOP did not prolong PFS in advanced, aggressive NHL.

Key words: aggressive non-Hodgkin's lymphoma, CHOP-14, CHOP-21, phase III trial

introduction

CHOP-21 [cyclophosphamide (CPA), doxorubicin (DXR), vincristine (VCR), and prednisone (PDN)] has remained a standard treatment for patients with aggressive non-Hodgkin's lymphoma (NHL) since 30 years [1]. However, CHOP-21 only cures 30%–50% of patients [2]. Several multidrug combinations with promising efficacy in phase II trials have been developed for improving outcome. However, several randomized phase III trials revealed that these regimens are not superior to CHOP-21 with respect to survival [3–6] partly due to lower dose intensities of CPA and DXR, key drugs for NHL, in the former than latter regimen [7].

Upfront high-dose chemotherapy with autologous stem-cell transplantation might be beneficial for high-intermediate and high-risk group patients [classified by the International Prognostic Index (IPI)] [8, 9]. Therefore, a dose-intensified strategy for NHL is still of interest to clinicians. Previously, we conducted a randomized phase II trial to investigate the effects of increasing dose intensity of CHOP along with interval shortening; biweekly CHOP (CHOP-14) was compared with dose-escalated CHOP in aggressive NHL patients [10]. Seventy aggressive NHL patients classified as high-intermediate or high-risk groups as per IPI randomly received either CHOP (eight courses; every 2 weeks) or dose-escalated CHOP (six courses; every 3 weeks). The biweekly regimen showed better complete response (CR) and 3-year progression-free survival (PFS) rates. Thus, CHOP-14 was suggested as a more suitable regimen to be evaluated in subsequent phase III trials.

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To determine whether dose-dense chemotherapy involving interval shortening of CHOP is superior to CHOP-21, the Lymphoma Study Group of the Japan Clinical Oncology Group conducted a phase III trial.

patients and methods

eligibility criteria

Forty-two centers participated in this trial. Inclusion criteria were as follows: previously untreated intermediate- or high-grade NHL according to the Working Formulation (D through H and J) [11]; clinical stage II–IV disease (Ann Arbor classification) [12]; age 15–69 years; Eastern Cooperative Oncology Group performance status 0–2; white blood cell count $\geq 3.0 \times 10^9$/l; absolute neutrophil count (ANC) $\geq 1.2 \times 10^9$/l; platelet count $\geq 75 \times 10^9$/l; aspartate aminotransferase (AST) and alanine aminotransferase levels less than or equal to five times the upper limit of the normal range; total bilirubin level ≤2.0 mg/dl; serum creatinine level ≤2.0 mg/dl; PaO_2 ≥65 mmHg; and normal electrocardiogram and cardiac function.

Exclusion criteria included any other malignancy, prior chemotherapy or radiotherapy, central nervous system involvement with lymphoma, HIV infection, positive test for hepatitis B virus surface antigen and/or hepatitis C virus antibody, pregnancy or breast-feeding, severe concomitant disease, or uncontrolled diabetes mellitus.

Written informed consent was obtained from all patients before enrollment, and the protocol was approved by the Protocol Review Committee of Japan Clinical Oncology Group (JCOG) and the Institutional Review Board of each participating center.

treatment

Patients were randomized at the JCOG Data Center after telephonic or fax registration to receive either CHOP-21 or CHOP-14 as per the minimization method of balancing the groups according to the institution, low/low-intermediate or high-intermediate/high-risk classification according to IPI, and informed consent available for *p53* gene analysis. CHOP-21 administered every 3 weeks consisted of CPA 750 mg/m^2 IV, DXR 50 mg/m^2 IV, VCR 1.4 mg/m^2 (maximum 2 mg) IV administered on day 1, and PDN 100 mg p.o. administered on days 1–5; same dosages of CHOP-14 were administered at every 2 weeks. Patients in the CHOP-14 arm received granulocyte colony-stimulating factor (G-CSF; filgrastim, lenograstim, or nartograstim) on days 6–13 or until their ANC was $>10 \times 10^9$/l. Patients in the CHOP-21 arm received G-CSF, if necessary. All patients in both study arms received eight courses of chemotherapy except those with progressive disease (PD) after two courses or no response (NR) after four courses when salvage chemotherapy was recommended.

If necessary, after eight courses of chemotherapy, patients were recommended for involved-field radiotherapy (dose 30–50 Gy), if they had initial bulky disease (masses of diameter > 5 cm) or if they only had a partial response (PR) in nonbulky disease.

response assessment

Tumor responses were assessed as per the World Health Organization (WHO) criteria [13] by clinical examination and computed tomography scan after two, four, six, and eight courses of chemotherapy and at 12 weeks after completing chemotherapy or radiotherapy and classified as CR, complete response unconfirmed (CRu), PR, NR, and PD.

statistical methods

All analyses were carried out according to an intent-to-treat principle, using SAS release 9.1 (SAS Institute, Cary, NC). The primary end point was PFS, which was calculated from the date of randomization to that of progression, relapse, or death from any cause. If patients survived without progression, PFS was censored on the latest date when no progression was confirmed. Secondary end points included overall survival (OS) calculated from the date of randomization to the date of death from any cause, CR rate (%CR), and toxicity. PFS and OS curves were generated using the Kaplan–Meier method. Toxicity was assessed as per the JCOG Toxicity Criteria (expanded and modified version of the National Cancer Institute Common Toxicity Criteria, version 1.0) [14]. All patient information forms were collected and managed at the JCOG Data Center where in-house interim monitoring was carried out, and the reports were semiannually reviewed by their Data and Safety Monitoring Committee.

This trial aimed to detect 10% improvement in 5-year PFS rates with CHOP-14 compared with CHOP-21, which was anticipated to have 5-year PFS rate of 50%. This study design required the enrollment of 410 patients with a one-sided α-level of 0.05 to attain 80% power over 4 years of accrual and 7 years of follow-up (including ineligibility and cases lost to follow-up). Two interim analyses were planned. The first involved comparing %CR after half of the patients had been assessed for response. However, blinded in-house monitoring showed poorer PFS than expected; the sample size was then amended to 330 patients, and the end point for the first interim analysis was changed from %CR to PFS.

Superiority of CHOP-14 was assessed by the one-sided log-rank test. Multiplicity was adjusted using an alpha-spending function of the O'Brien–Fleming type. To summarize the difference between the two arms at interim analysis, hazard ratios (HRs) with confidence intervals (CIs) were calculated [15]. If CHOP-14 proved inferior, the predictive distribution of HR [16] was used to decide whether to stop the trial for futility monitoring. Updated data and estimate HRs between the two arms were analyzed by Cox regression analysis.

central pathology review

Collected biopsy specimens (290 specimens) of enrolled patients were forwarded for central pathology review. Four hematopathologists classified them according to the Working Formulation and WHO classification (third edition) [17].

results

interim analysis

The first planned interim analysis was carried out in December 2002. Because CHOP-14 was deemed highly unlikely to be superior to CHOP-21 with respect to PFS, the trial was terminated early following recommendations by the JCOG Data and Safety Monitoring Committee on 18 December 2002. At the first interim analysis of 286 patients, median PFS was 33.9 and 24.3 months for patients in CHOP-21 ($n = 143$) and CHOP-14 ($n = 143$) arms, respectively (one-sided log-rank $P = 0.68$). The 2-year PFS rate was 54.4% (95% CI 45.0% to 63.7%) in the CHOP-21 arm and 51.1% (95% CI 41.4% to 60.8%) in the CHOP-14 arm with a HR of 1.10 (95% CI 0.76% to 1.57%). Two-year OS rates were 73.8% (95% CI 65.4% to 82.3%) and 74.8% (95% CI 66.1% to 83.5%) in CHOP-21 and CHOP-14 arms, respectively.

patient characteristics

Between February 1999 and December 2002, 323 enrolled patients were randomly assigned to CHOP-21 (161 patients) and CHOP-14 arms (162 patients). Patient characteristics in both groups were well balanced (Table 1). Among the 323

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Table 1. Patients' characteristics

	CHOP-21		CHOP-14		Total	%
	n	%	*n*	%		
Number of patients	161	49.8	162	50.2	323	
Age						
Median (range)	58 (18–69)		57 (17–69)		57 (17–69)	
<61	103	64.0	111	68.5	214	66.3
≥61	58	36.0	51	31.5	109	33.7
Gender						
Male	94	58.4	96	59.3	190	58.8
Female	67	41.6	66	40.7	133	41.2
ECOG performance status						
0	79	49.1	88	54.3	167	51.7
1	68	42.2	61	37.7	129	39.9
2	14	8.7	13	8.0	27	8.4
Number of extranodal sites						
0, 1	127	78.9	132	81.5	259	80.2
>2	34	21.1	30	18.5	64	19.8
LDH greater than normal	80	49.7	74	45.7	154	47.7
Stage						
I[a]	3	1.9	1	0.6	4	1.2
II	56	34.8	58	35.8	114	35.3
III	42	26.1	43	26.5	85	26.3
IV	60	37.3	60	37.0	120	37.2
Bulky mass	82	50.9	86	53.1	168	52.0
IPI risk group						
Low	65	40.4	78	48.1	143	44.3
Low-intermediate	51	31.7	45	27.8	96	29.7
High-intermediate	36	22.4	26	16.0	62	19.2
High	9	5.6	13	8.0	22	6.8
Working formulation						
Institutional [consensus] diagnosis						
Small lymphocytic	[2]		[0]		[2]	
Follicular small cleaved	[1]		[3]		[4]	
Follicular mixed	[6]		[5]		[11]	
Follicular large	17 [8]		17 [13]		34 [21]	
Diffuse small cleaved	8 [6]		9 [6]		17 [12]	
Diffuse mixed	21 [13]		20 [13]		41 [26]	
Diffuse large	112 [93]		111 [94]		223 [187]	
Immunoblastic	3 [0]		4 [4]		7 [4]	
Small noncleaved	0 [2]		1 [2]		1 [4]	
Miscellaneous	[3]		[5]		[8]	
Others	[6]		[5]		[11]	
WHO classification						
MCL	2		2		4	
FL	11		12		23	
FL, follicular large plus diffuse large	4		9		13	
MZBCL	4		2		6	
DLCL	88		99		187	
BCL, unclassified	1		1		2	
BCL, low grade	4		2		6	
HL	4		3		7	
Miscellaneous	2		3		5	
NK/T lymphoma	2		1		3	
AILT	6		5		11	
PTCL	9		7		16	
ATL	1		1		2	
ALCL	2		2		4	

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Table 1. (*Continued*)

	CHOP-21		CHOP-14		Total	%
	n	%	*n*	%		
T-cell lymphoma, unclassified	0		1		1	
Not collected	21		12		33	

[a]Ineligible, but one of four patients was treated as eligible.

MCL, mantle cell lymphoma; FL, follicular lymphoma; MZBCL, marginal zone B-cell lymphoma; DLCL, diffuse large cell lymphoma; BCL, B-cell lymphoma; HL, Hodgkin lymphoma; NK, natural killer; AILT, angioimmunoblastic T-cell lymphoma; PTCL, peripheral T-cell lymphoma; ATL, adult T-cell leukemia-lymphoma; ALCL, anaplastic large cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

patients, 8 were ineligible [3, incorrect histopathological diagnosis immediately after registration (2 with adult T-cell leukemia–lymphoma and 1 with follicular mixed-type lymphoma); 3, stage I disease; 1, complicated gastric cancer; and 1, no measurable lesion]. Of 290 patients whose biopsy samples were reviewed, 38 (13.1%) (18, CHOP-21 and 20, CHOP-14) were considered ineligible.

After chemotherapy, involved-field radiotherapy (dose 30–50 Gy) was administered to 58 patients (28, CHOP-21 and 30, CHOP-14) with initial bulky disease and 7 with PR and with no initial bulky mass for residual disease (2, CHOP-21 and 5, CHOP-14).

toxic effects

Collected case report forms of 320 patients (including ineligible patients) were used for evaluating toxic effects (Table 2). At least one episode of grade 4 neutropenia was experienced by 83.6% and 52.2% patients in CHOP-21 and CHOP-14 arms, respectively. While 12.5% and 20.6% patients in CHOP-21 and CHOP-14 arms, respectively, experienced grade 3 anemia (hemoglobin < 8 g/dl). Only one patient experienced grade 4 thrombocytopenia.

Nonhematologic toxic effects were mild and equivalent in both arms. However, treatment in the CHOP-21 arm was discontinued for four patients [one, decreased left ventricular ejection fraction (<40%); one, hypertension with Wallenberg's syndrome; one, gastric perforation; and one, amebic abscesses in the intestine and liver]. Protocol treatment was discontinued for seven patients (three, pneumonitis; three, ≥grade 2 arrhythmias; and one, a vertebral compression fracture) in the CHOP-14 arm.

After the seventh course of CHOP-14, one patient died suddenly but the cause of death could not be determined. In the CHOP-14 arm, one male patient developed Pneumocystis pneumonia immediately after the eighth course of chemotherapy and died of respiratory failure.

Twenty-nine secondary malignancies cases (CHOP-21 arm: 8 and CHOP-14 arm: 21) were also observed. Median age at lymphoma diagnosis was 59 years (range 32–68 years) and 60 years (range 41–69 years) in CHOP-21 and CHOP-14 arms, respectively. Three and eight patients in CHOP-21 and CHOP-14 arms were >60 years. In the CHOP-21 arm, the cases included non-small-cell lung cancer ($n = 1$), breast cancer ($n = 1$), gastric cancer ($n = 2$), pancreatic cancer ($n = 2$), prostate cancer ($n = 1$), and diffuse large B-cell lymphoma ($n = 1$). Only one pancreatic cancer patient received consolidative radiotherapy. One patient whose lymphoma had progressed during CHOP-21 treatment received allogeneic hematopoietic stem-cell transplantation, and the patient later developed non-small-cell lung cancer. Lymphoma relapse was not observed among other patients. In the CHOP-14 arm, the cases included thyroid cancer ($n = 1$), non-small-cell lung cancer ($n = 2$), breast cancer ($n = 2$), gastric cancer ($n = 3$), pancreatic cancer ($n = 1$), colon cancer ($n = 3$), uterine cervical cancer ($n = 1$), prostate cancer ($n = 1$), Ewing's sarcoma ($n = 1$), mantle cell lymphoma ($n = 1$), and myelodysplastic syndrome ($n = 5$). Every patient with breast cancer, mantle cell lymphoma, and colon cancer received consolidative radiotherapy. Lymphoma relapsed in three cases. One patient received salvage and high-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation and developed myelodysplastic syndrome 23 months after CHOP-14 treatment. Other patients developed gastric and colon cancer after salvage chemotherapy. Lymphoma relapse was not observed in patients with myelodysplastic syndrome;

Table 2. Toxic effects

	CHOP-21, $n = 160$	CHOP-14, $n = 160$
Leukopenia (% grade 4)	47.5	35.0
Neutropenia (% grade 4)	83.6	52.2
Anemia (% grade 3)	12.5	20.6
Thrombocytopenia (% grade 4)	0.6	0.6
T-bil (% grade 3, 4)	2.5	0
AST (% grade 3, 4)	3.1	0
ALT (% grade 3, 4)	5.0	3.1
Creatinine (% grade 3, 4)	0	0.6
Hyperglycemia (% grade 3, 4)	2.0	3.2
Arrhythmia (% grade 3, 4)	1.3	0.6
Cardiac ischemia (% grade 3, 4)	0.6	0.7
Infection (% grade 3, 4)	3.8	3.8
Neurotoxicity—sensory (% grade 3, 4)	1.3	5.7
Neurotoxicity—motor (% grade 3, 4)	1.3	2.5
Constipation (% grade 3, 4)	1.3	1.3

Toxicity forms collected 320 patients.

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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they received no additional therapy. In the CHOP-14 arm, the tendency toward development of secondary malignancies, including myelodysplastic syndrome, was significant.

treatment interval and dose intensity

To confirm treatment compliance, we assessed actual treatment duration, course interval, and actual dose administered. Total treatment duration was calculated as the duration from day 1 of the first course to day 1 of the eighth course. The planned duration of CHOP-21 and CHOP-14 treatment were 148 and 99 days, respectively. The relative dose (%) was calculated as the dose actually administered divided by the total dose planned for all eight courses.

The course interval was 21 days for 79.3% patients and 14 days for 83.2% patients in CHOP-21 and CHOP-14 arms, respectively. The treatment duration in each arm almost matched the planned duration. Figure 1 shows the distribution of the achievement quotient for planned CPA and DXR doses. In the CHOP-21 arm, median relative doses of CPA and DXR were 97.2% (actual dose range 752–6285 mg per body weight) and 99.4% (actual dose range 50–419 mg/body weight), respectively. In the CHOP-14 arm, median relative doses of CPA and DXR were 98.1% (actual dose range 724–6259 mg/body weight) and 99.6% (actual dose range 50–411 mg/body weight), respectively. With patients stratified by age (>60 or <60 years), in elderly patients, median relative doses of CPA and DXR were 97.1% and 99.2% in the CHOP-21 arm and were 97.4% and 99.0% in the CHOP-14 arm. In younger patients, median relative doses of CPA and DXR were 97.5% and 99.5% in the CHOP-21 arm and were 98.2% and 99.8% in the CHOP-14 arm. Thus, small variations from the planned course interval and dosage were observed, but compliance was good in both arms.

responses

Responses were assessed 12 weeks after chemotherapy or radiotherapy. Among all randomized patients, CR (including CRu) was observed in 61.5% (95% CI 53.5% to 69.0%) and 66.7% (95% CI 58.8% to 73.9%) patients in CHOP-21 and CHOP-14 arms, respectively (Table 3). Similar results were observed in eligible patients, and no significant difference was observed between the two arms.

survival

Figure 2 shows the PFS and OS curves for all randomized patients. At 7-year follow-up after enrollment termination, no substantial differences were observed in PFS and OS between the two arms. Median PFS was 2.8 and 2.6 in CHOP-21 and CHOP-14 arms, respectively. Eight-year PFS rates were 41.5% (95% CI 33.7% to 49.1%) and 38.4% (95% CI 30.5% to 46.1%) in CHOP-21 and CHOP-14 arms, respectively ($P = 0.79$, HR

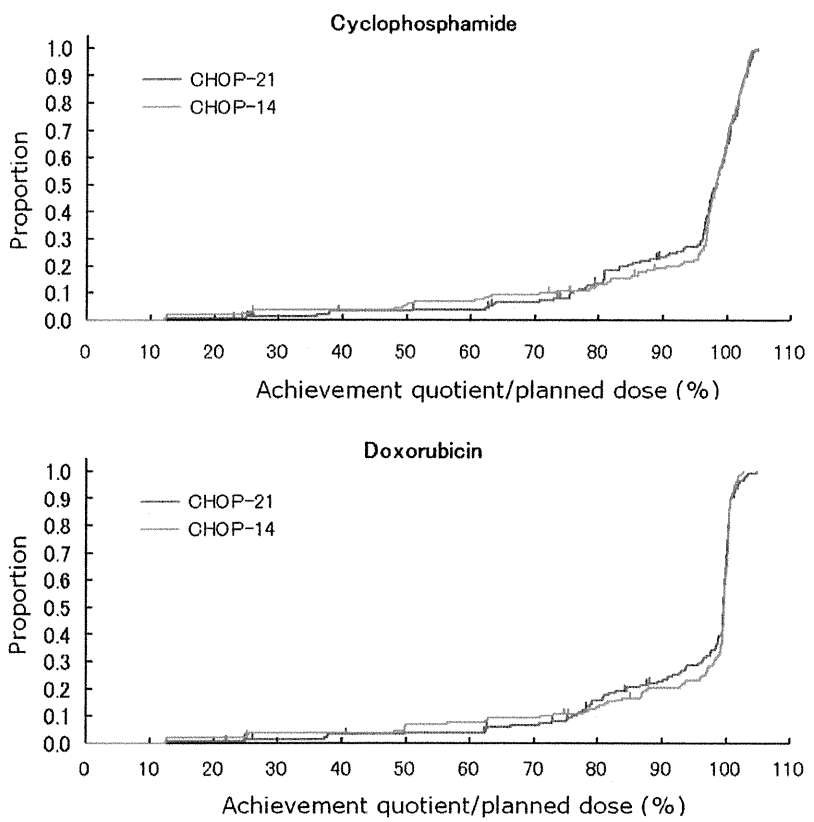

Figure 1. Distribution of the achievement quotient for planned doses of cyclophosphamide and doxorubicin.

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1.04, 95% CI 0.78% to 1.38%), and 8-year OS rates were 55.9% (95% CI 47.3% to 63.7%) and 55.4% (95% CI 46.9% to 63.0%) in CHOP-21 and CHOP-14 arms, respectively ($P = 0.82$, HR 1.04, 95% CI 0.75% to 1.45%).

Subgroup analyses were also carried out for risk groups classified as per IPI and for patients stratified in two age groups; no remarkable differences were observed between the two arms for each subgroup (Figure 3).

Among patients with diffuse large B-cell lymphoma (the major subtype of aggressive NHL identified by central pathological review), 8-year PFS rates were 47.5% (95% CI 36.3% to 57.9%) and 44.1% (95% CI 32.8% to 54.8%) in CHOP-21 and CHOP-14 arms, respectively, and 8-year OS rates were 55.4% (95% CI 42.9% to 66.2%) and 55.4% (95% CI 43.0% to 66.1%) in CHOP-21 and CHOP-14 arms, respectively.

Table 3. Response after completion of the protocol treatment

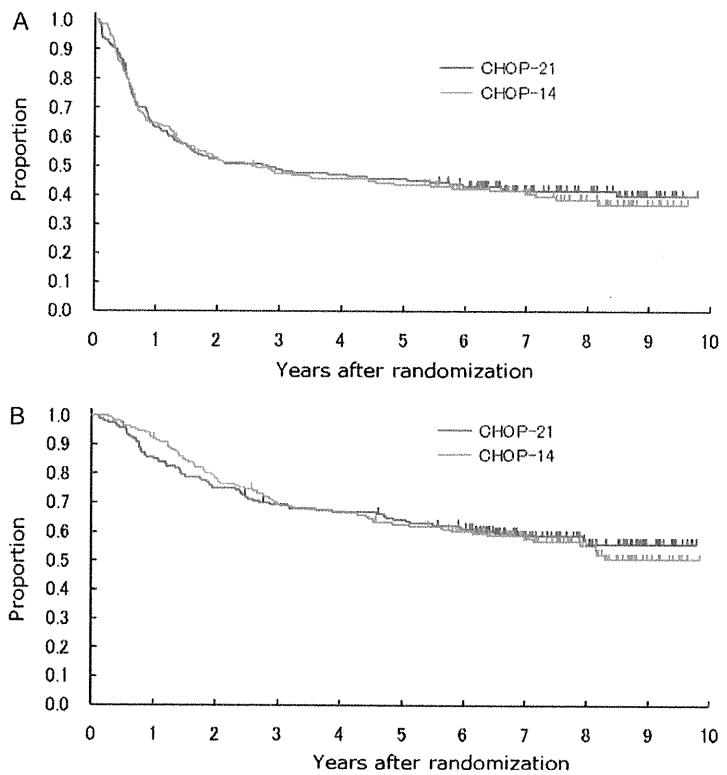
	CHOP-21 (%), $n = 161$	CHOP-14 (%), $n = 162$
CR	38.5	44.4
CRu	23.0	22.2
PR	0	0
NR	0	0
PD	12.4	9.3
Not evaluable	1.2	0
%CR (CR + CRu)	61.5	66.7
95% CI	53.5–69.0	58.8–73.9

CI, confidence interval, CR, complete response; CRu, complete response unconfirmed, %CR, CR rate; NR, no response; PD, progressive disease; PR, partial response.

conclusions

This trial failed to demonstrate the superiority of CHOP-14 over CHOP-21 for the treatment of aggressive NHL. PFS and OS after CHOP-14 were lower than those after CHOP-21 at the first interim analysis, and the trial was terminated early because the estimated predictive probability that CHOP-14 would be significantly superior to CHOP-21 was only 19%, even if the trial was continued. This result did not change even during long-term follow-up.

During treatment, there was no tendency for the interval of CHOP-14 to be postponed. No differences in planned dose and



arm	n	Median PFS	Median OS	8-year PFS (95%CI)	8-year OS (95%CI)
CHOP-21	161	2.8 years	not reached	41.5% (33.7%–49.1%)	55.9% (47.3%–63.7%)
CHOP-14	162	2.6 years	not reached	38.4% (30.5%–46.1%)	55.4% (46.9%–63.0%)

Figure 2. Progression-free survival (PFS) and overall survival (OS) curves for all randomized patients. (A) PFS curve and (B) OS curve.

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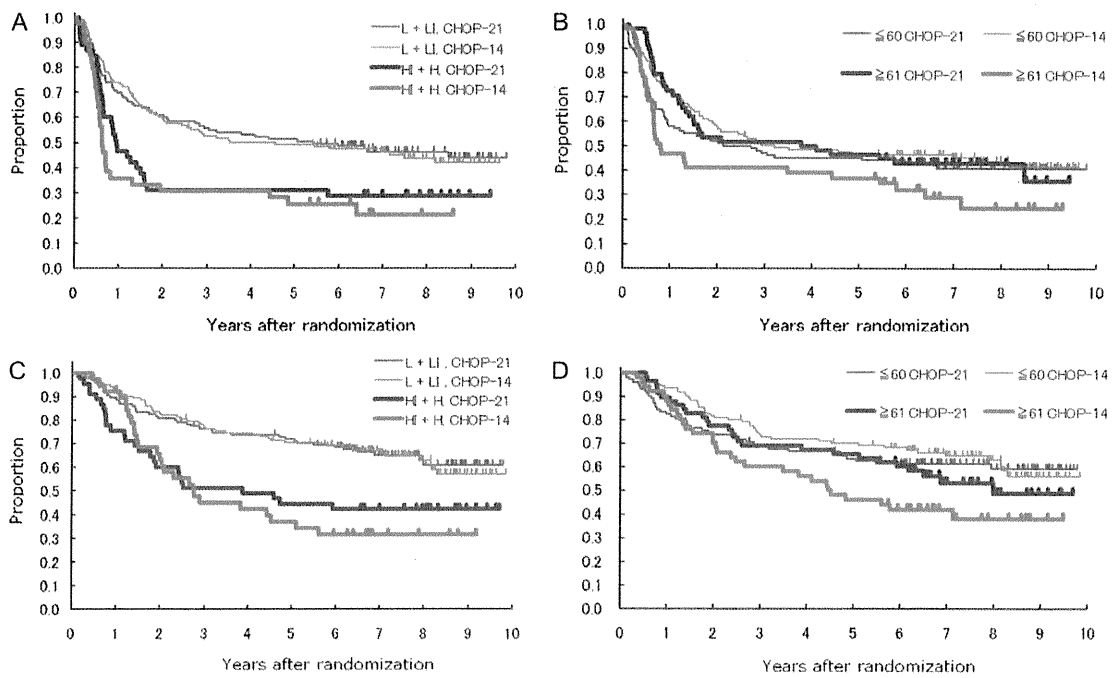

			n	event	HR of CHOP-14 vs CHOP-21	95%CI of HR	
PFS	L/LI	CHOP-21	116	62			
		CHOP-14	123	68	1.019	0.722	1.438
	HI/H	CHOP-21	45	32			
		CHOP-14	39	30	1.284	0.779	2.116
PFS	AGE • 60	CHOP-21	103	60			
		CHOP-14	111	62	0.851	0.597	1.214
	AGE > 60	CHOP-21	58	34			
		CHOP-14	51	36	1.623	1.014	2.595
OS	L/LI	CHOP-21	116	41			
		CHOP-14	123	46	1.018	0.668	1.550
	HI/H	CHOP-21	45	26			
		CHOP-14	39	26	1.150	0.667	1.983
OS	AGE • 60	CHOP-21	103	40			
		CHOP-14	111	42	0.888	0.576	1.369
	AGE > 60	CHOP-21	58	27			
		CHOP-14	51	30	1.488	0.884	2.506

Figure 3. Progression-free survival (PFS) and overall survival (OS) curves for all randomized patients of the risk group classified as per International Prognostic Index (IPI) and for all randomized patients classified as per age. (A) PFS curve for the risk group classified as per IPI, (B) PFS curve for patients classified as per age, (C) OS curve for the risk group classified as per IPI and (D) OS curve for patients classified as per age.

accumulation ratios of key drugs were observed between the two arms, and treatment compliance was not only equivalent but also good in both arms. We therefore do not consider poor compliance, the cause of the lack of difference in efficacy between the two arms. Only 8.4% of the patients had a performance status of 2, and 26% of the patients belonged to high-intermediate and high-risk groups. These values were slightly low, thus implying that more patients with good prognoses were enrolled. However, patient characteristics did not differ completely, and subgroup analysis showed that survival in the high-risk group tended to be equivalent between the two arms. Thus, patient population may not have caused a bias in the study end points.

Other trials using dose-dense chemotherapy have been conducted by two groups. The German High-Grade Non-Hodgkin Lymphoma Study Group reported that CHOP-14 showed higher event-free survival (EFS) and OS in elderly patients than CHOP-21 in the NHL-B2 trial [18], and CHOEP-21 (CHOP-21 with etoposide) significantly improved survival compared with CHOP-21 in younger patients with normal lactate dehydrogenase (LDH) in the NHL-B1 trial [19]. As for the difference of these results, Pfreundschuh and Loeffler [20], in response to Coiffier and Salles [21], pointed out that the

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schedule of CHOP-14 in our trial was well maintained; however, DXR doses were different from those in the NHL-B2 trial. In our trial, 24% patients received <90% of the planned dose of DXR, and 16% of patients received <80%, whereas in the NHL-B2 trial, only 11% and 9% of patients received <90% and 80% of DXR, respectively. Therefore, Pfreundschuh and Loeffler [20] argued that both planned dose and treatment interval must be maintained to preserve the superiority of the two-weekly regimen over the three-weekly regimen. However, results from cumulative dose analyses may differ according to the manner in which cases of early discontinuation of treatment (early off-treatment) are treated. Because relative dose curves in NHL-B1 and -B2 trials do not reflect the early off-treatment rate [18, 19, 22], Pfreundschuh's argument may not be derived from intention to treat analysis. In our trial, the cumulative percentage of patients receiving <90% of the planned dose of DXR decreases from 20% to 9% if we do not include the early off-treatment rate. Thus, comparison of results using different definitions is irrelevant. In NHL-B1 and -B2 trials, although both total chemotherapy duration and relative dose intensity tended to be better maintained in younger than elderly patients [22], the dose-dense regimen was not always superior to the 3-weekly regimen for younger patients. Even our trial showed a similar tendency. Moreover, no differences were maintained between our two treatment arms in terms of planned DXR or CPA doses administered or in any other background variable, and comparisons between the treatment arms were reliable.

In exploratory subgroup analysis, unlike in the NHL-B2 trial, CHOP-14 showed no survival advantage for elderly patients and appeared less effective in terms of OS and PFS. The planned CPA and DXR doses for elderly patients were well maintained in CHOP-14 and CHOP-21 arms. Secondary malignancies in elderly patients were observed more often in the CHOP-14 arm, but the cause of death in elderly patients was mostly due to lymphoma in both arms. Consequently, poorer outcomes were not derived from dose reduction of key drugs and secondary malignancies. On the other hand, subgroup analysis indicated that the efficacy of CHOP-14 was slightly greater than that of CHOP-21 in terms of OS and PFS in patients <60 years. In multivariate analysis using Cox regression, elevated LDH was identified as a negative prognostic factor in terms of both PFS and OS (Table 4). Age-based patient characteristics showed that the number of elderly patients with elevated LDH was greater in the CHOP-14 arm than in the CHOP-21 arm and that of younger patients with elevated LDH was lower in the CHOP-14 arm than in the CHOP-21 arm (Table 5). Thus, these deviations may have somewhat influenced our results. However, these results were based on a small number of patients and are not statistically significant. In the NHL-B1 trial, CHOP-14 did not exceed CHOP-21 in EFS but slightly exceeded CHOP-21 in OS. Furthermore, the Dutch–Belgian Group conducted a randomized trial comparing Intensified CHOP (I-CHOP), consisting of dose-dense chemotherapy, with CHOP-21, and reported that I-CHOP improved OS in low-intermediate risk patients according to age-adjusted IPI [23]. These results do not show similar tendencies, but taken together, dose-dense chemotherapy may be beneficial for some patients.

Frequency of secondary malignancies in the CHOP-14 arm was also determined in this trial. In the CHOP-14 arm, 9.9% and 3.1% patients developed solid tumors and myelodysplatsic syndrome, respectively, whereas in the CHOP-21 arm, 5.5% patients developed solid tumors and no patient developed myelodysplastic syndrome. Radiation, alkylating agents, and high-dose chemotherapy influence secondary malignancy development, and epipodophyllotoxin, G-CSF, and greater dose intensity are particularly involved with secondary myelodysplastic syndrome and acute myeloid leukemia [24–27]. Secondary myelodysplastic syndrome development might be greatly affected by G-CSF because such developments were only observed in the CHOP-14 arm. In terms of solid tumors, no differences were observed between the two arms with regard to patient background, such as receiving radiotherapy, dose of alkylating agent, and use of etoposide during or after treatment; thus, preexisting factors are not responsible for these results. Because dose-dense chemotherapy may cause more secondary solid tumors, long-standing careful follow-up of patients is needed.

Our trial did not use rituximab in combination with CHOP because rituximab was unavailable under the Japanese National Health Insurance at the time of patient enrollment. Since the superiority of this combination therapy over CHOP alone has been proven for elderly and younger low-risk patients with diffuse large B-cell lymphoma [28, 29], it has been recognized as a current standard treatment worldwide. The efficacy of dose-dense chemotherapy combined with rituximab remains yet to be clarified. Delarue et al. [30] recently reported that CHOP-14 was not superior to CHOP-21 plus rituximab in an interim analysis. A similar result was reported by Pfreundschuh et al. [29], who noted that the benefit achieved with etoposide plus CHOP-21 was absent for CHOP-21 plus rituximab, and he reasoned that this was due to the equalizing effect of rituximab.

Table 4. Result of multivariate analysis using COX regression

	PFS			OS		
	P	HR	95% CI	*P*	HR	95% CI
CHOP-21 versus CHOP-14	0.6074	1.078	0.810–1.433	0.5614	1.104	0.790–1.543
Stage I, II versus III, IV	0.0002	1.922	1.369–2.698	0.1052	1.389	0.933–2.068
PS 0, 1 versus 2	0.0393	1.637	1.024–2.616	0.0309	1.773	1.054–2.982
Age <60 versus >61	0.2506	1.191	0.884–1.603	0.0135	1.539	1.093–2.166
Extranodal disease 0, 1 versus >2	0.3834	1.171	0.821–0.671	0.1075	1.389	0.931–2.071
LDH normal versus elevated	0.0098	1.486	1.100–2.007	0.0017	1.768	1.239–2.524

CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

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Table 5. Patients' characteristics according to age

	Age ≤ 60				Age ≥ 61			
	CHOP-21		CHOP-14		CHOP-21		CHOP-14	
	n	%	*n*	%	*n*	%	*n*	%
Stage								
I, II	37	35.9	42	37.8	22	37.9	17	33.3
III, IV	66	64.1	69	62.2	36	62.1	34	66.7
Performance status								
0, 1	92	89.3	103	92.8	55	94.8	46	90.2
2	11	10.7	8	7.2	3	5.2	5	9.8
Extranodal disease								
0.1	79	76.7	91	82.0	48	82.8	41	80.4
≥2	24	23.3	20	18.0	10	17.2	10	19.6
Lactate dehydrogenase								
Normal	51	49.5	65	58.6	30	51.7	23	45.1
Elevated	52	50.5	46	41.4	28	48.3	28	54.9

In the rituximab era, the efficacy of dose-dense chemotherapy may thus not be as significant as before.

Here, CHOP-14 reduced the frequency of febrile neutropenia and shortened the total treatment duration. However, it did not improve survival, was more inconvenient to use, and was significantly more often associated with secondary malignancies. Thus, CHOP-14 is not suitable as a standard regimen to replace CHOP-21, and dose-dense chemotherapy with shortened treatment interval is not useful for improving the outcome in aggressive NHL patients.

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disclosure

The authors declare no conflict of interest.

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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

平成23年度 厚生労働科学研究費補助金 第3次対がん総合戦略研究事業
「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」

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＜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。

＜お願い＞

このアンケートは、がん診療を受けられている皆様を対象にしております。

○ 日数や金額などをおたずねする項目では、過去の領収書などを参考にしながらお答え下さい。正確にわからない場合は、おおよそで結構です。

○ お答えいただいたアンケートは、返信用の封筒でお送り下さい。
その際にアンケートおよび返信用封筒にお名前を書いていただく必要はありません。

○ ご自身の診断名、病期、治療内容の情報の提供に同意される場合は、同意書に署名いただきます。同意を受けた後に、医師から提供されたデータを突合するためこの調査票に整理番号が記されていますが、個人が特定されることはありません。
またアンケートに参加しなくても、今後の診療に不利益は生じません。

○ まことに恐れ入りますが、お答えいただいたアンケートは、1週間程度でご返送下さい。
何とぞ、よろしくお願い申し上げます。

記入日　平成　　年　　月　　日

＜お問い合わせ先＞
〒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、尾形倫明
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No.

がん診療の経済的な負担に関するアンケート調査

1．現在がんに関してお困りの事がありますか。ある場合は重要なもの3つまで○をつけて下さい。

治療・心身の面 □ない □ある（下記より3つまで○）	経済的な面 □ない □ある（下記より3つまで○）	社会的な面 □ない □ある（下記より3つまで○）
1　再発・転移	1　医療費（保険診療）	1　家族との関係
2　後遺症・副作用	2　医療費（自費診療）	2　友人・隣人との関係
3　外見の変化	3　通院にかかる交通費	3　医師・看護師などとの関係
4　気分が落ち込む	4　民間療法の費用	4　仕事
5　夜眠れない	5　補正具・補装具などの費用	5　財産
6　食欲がない	6　介護費用	6　趣味・生き甲斐
7　食事に気をつかう	7　収入の減少	7　定期的受診の煩わしさ
8　排尿・排便	8　貯蓄の目減り	8　医療への依存
9　その他（　　）	9　その他（　　）	9　がん情報の入手
		10　その他（　　）

2．医療保険の自己負担割合は、何割ですか。あてはまるものに○をつけて下さい。

3割	2割	1割	自己負担なし

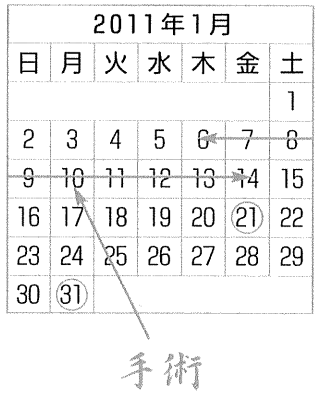
3．がんに関して、過去1年間の支出入を、領収書・家計簿等を見ながらご記入下さい。
該当しない場合は0円と記入して下さい。

病院や薬局の窓口で支払った金額	入院分	円
	外来分	円
通院の際の往復交通費（宿泊費を含む・1回あたり）		円
健康食品や民間療法の支出		円
その他の支出（補装具など）		円
がん医療に関する民間保険	払った保険料	円
	受け取った給付金	円
高額療養費制度	現在の自己負担限度額	円
	戻ってきた金額	円
医療費還付として戻ってきた税金（昨年1年間）		円

4．過去１年間にこの病気で入院された期間を ←→ で記入し入院の理由（手術・検査等）を書き入れて下さい。
また、外来通院された日には○をつけて下さい。
わが国における適切な入院日数、通院頻度を検討する資料となるものです。

過去１年間の入院のべ日数	日
過去１年間の外来通院回数	回

〈記入例〉



2010年（昨年）

2010年9月

日	月	火	水	木	金	土
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

2010年10月

日	月	火	水	木	金	土
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

2010年11月

日	月	火	水	木	金	土
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

2010年12月

日	月	火	水	木	金	土
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

2011年（今年）

2011年1月

日	月	火	水	木	金	土
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

2011年2月

日	月	火	水	木	金	土
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28					

2011年3月

日	月	火	水	木	金	土
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

2011年4月

日	月	火	水	木	金	土
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

2011年5月

日	月	火	水	木	金	土
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

2011年6月

日	月	火	水	木	金	土
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

2011年7月

日	月	火	水	木	金	土
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

2011年8月

日	月	火	水	木	金	土
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

2011年9月

日	月	火	水	木	金	土
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

2011年10月

日	月	火	水	木	金	土
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

2011年11月

日	月	火	水	木	金	土
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

2011年12月

日	月	火	水	木	金	土
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

5．治療を振り返って、入院や外来について思ったことで、あてはまる番号１つに○をつけて下さい。

	大変満足	やや満足	やや不満	大変不満	その理由
診療に関する説明内容	1	2	3	4	( )
診療に関する説明時間	1	2	3	4	( )
入院期間（該当者のみ）	1	2	3	4	( )
外来通院回数	1	2	3	4	( )
外来での待ち時間	1	2	3	4	( )
診察時間	1	2	3	4	( )
診察内容	1	2	3	4	( )
検査回数	1	2	3	4	( )
医師の対応	1	2	3	4	( )
看護師の対応	1	2	3	4	( )
窓口の対応	1	2	3	4	( )
病院までの交通の便	1	2	3	4	( )

6．ご自身について

年齢	歳	性別	男　女	居住地	都道府県

7．現在の病気について

部位・病名		病期	I　II　III　IV　不明
初めてがんと診断された日	平成 昭和　年　月　日	再発	有　無

8．がん医療の経済的負担について、自由にご意見をお書き下さい。

ご協力、どうもありがとうございました。

医師記入項目（問１～問５）

１．下記項目を記入して下さい。

年　齢	歳	性　別	男　女	
部位・病名（　　）□ 原発　□ 再発				ICD-10（　　）
Clinical Stage（　　）必ずご記入下さい				病期　T（　）N（　）M（　）

２．初めてがんと診断した日　西暦　　年　　月　　日　□ 自施設診断　□ 他施設診断（紹介）

３．診断から現在までに手術を行った場合に☑をつけ、その内容と時期を記入して下さい。

□ 手術（術式）	実施
（　　）	年　月　日
（　　）	年　月　日

過去１年程度に行った治療全てに☑をつけ、その内容と時期を記入して下さい。

□ 化学療法・分子標的治療（１レジメン毎）	開始	終了（治療中の場合は記入不要）
（　　）	年　月　日	年　月　日
（　　）	年　月　日	年　月　日
（　　）	年　月　日	年　月　日
□ 放射線療法（方式）		
（　　）	年　月　日	年　月　日
（　　）	年　月　日	年　月　日
□ その他		
（　　）	年　月　日	年　月　日
（　　）	年　月　日	年　月　日

４．下記項目に該当する場合は☑をつけて下さい。

□ 治験　□ 先進医療　□ 生活保護　□ 公費

５．病歴についての特記事項

No

表1. 回答者の属性

性別	全体	2,752
	男	1,141 (41.5%)
	女	1,611 (58.5%)
年齢（歳）	全体	63.3 ± 11.9 (n=2,749)
	男	67.7 ± 10.6 (n=1,140)
	女	60.3 ± 11.9 (n=1,608)
初回診断時期（ヶ月前）		38.6 ± 58.1 (n=2,403)
入院日数		32.8 ± 38.3 (n=1,592)
通院回数		19.6 ± 16.5 (n=2,394)

図1. 自己負担額と償還額（年間）

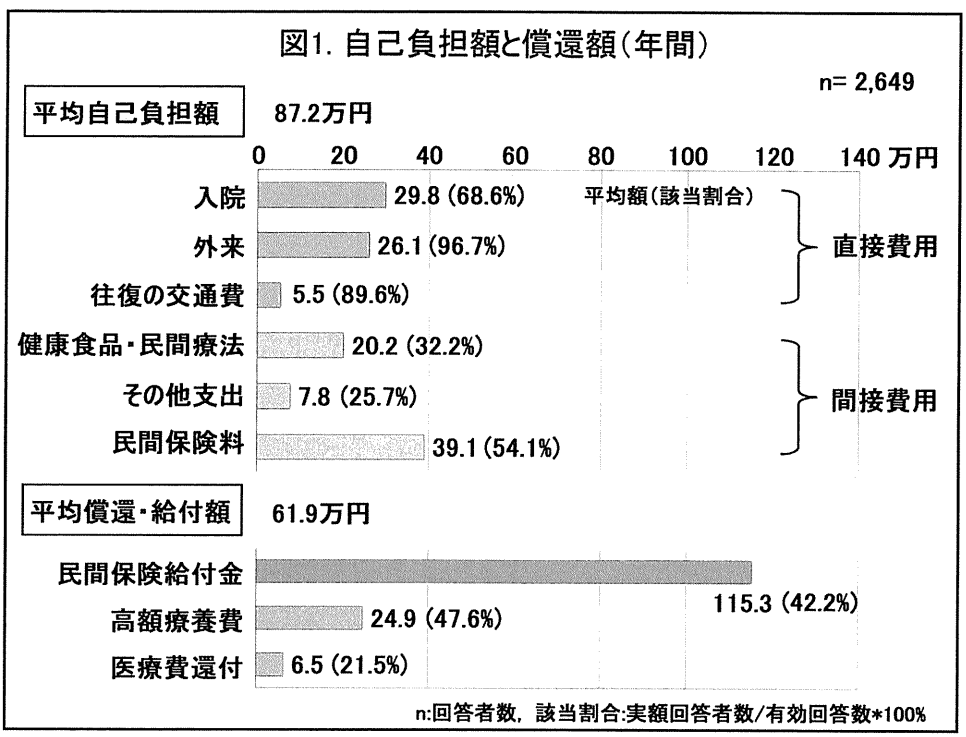


表2. 回答者の属性（医師・患者突合データ）

性別	全体	2,089
	男	838 (40.1%)
	女	1,251 (59.9%)
年齢（歳）	全体	63.3 ± 11.7 (n=2,086)
	男	67.6 ± 10.6 (n=837)
	女	60.5 ± 11.6 (n=1,248)
初回診断時期（ヶ月前）（医師データ）		30.3 ± 36.2 (n=1,865)
入院日数		32.3 ± 36.5 (n=1,198)
通院回数		19.3 ± 16.5 (n=1,832)

図2-1. 部位・病名（医師データ）