continued. Tumour lesions were assessed radiologically at baseline, week 4, week 7, every 6 weeks from week 7 to 18 months, and every 12 weeks thereafter until disease progression according to RECIST 1.1.

	Erlotinib plus bevacizumab group (n=75)	Erlotinib alone group (n=77)
Age (years)		
Median	67·0 (59–73)	67·0 (60–73)
<75	63 (84%)	62 (81%)
≥75	12 (16%)	15 (19%)
Sex		
Male	30 (40%)	26 (34%)
Female	45 (60%)	51 (66%)
Smoking status		
Never smoker	42 (56%)	45 (58%)
Former light smoker	9 (12%)	6 (8%)
Other	24 (32%)	26 (34%)
ECOG performance status		
0	43 (57%)	41 (53%)
1	32 (43%)	36 (47%)
Histopathological classification		
Adenocarcinoma	74 (99%)	76 (99%)
Large-cell carcinoma	0	1 (1%)
Adenosquamous carcinoma	1 (1%)	0
Clinical stage at screening		
IIIB	1 (1%)	0
IV	60 (80%)	62 (81%)
Postoperative recurrence	14 (19%)	15 (19%)
***EGFR* mutation type**		
Exon 19 deletion	40 (53%)	40 (52%)
Exon 21 Leu858Arg mutation	35 (47%)	37 (48%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline demographics and clinical characteristics**

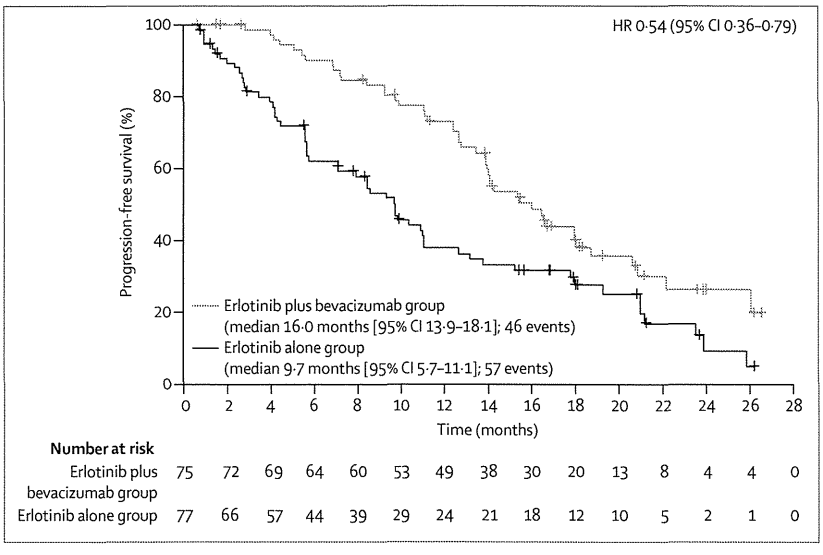

Figure 2: **Progression-free survival, as determined by independent review committee, in the modified intention-to-treat population**
HR=hazard ratio.

Patient-reported outcomes were assessed with the Functional Assessment of Cancer Therapy for patients with Lung cancer (FACT-L) scale until disease progression. An independent review committee of clinicians and radiologists masked to treatment assignment reviewed all tumour images and determined tumour response and progression status. Laboratory studies including blood and urine tests were done at days 1, 8, and 15 in cycles 1 and 2, and day 1 in cycle 3 and thereafter. Adverse events were monitored throughout the study period and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) version 4.03.

Outcomes

The primary endpoint was progression-free survival, as determined by an independent review committee. Secondary endpoints were overall survival, tumour response (the proportion of patients with an objective response and disease control, and duration of response) according to RECIST 1.1, quality of life, symptom improvement measured by the FACT-L scale, and safety profile.

Statistical analysis

A median progression-free survival of 13 months was estimated for the erlotinib alone group, and 89 events were deemed necessary to detect a hazard ratio (HR) of 0·7 in favour of erlotinib plus bevacizumab, with a one-sided significance level of 0·2 and a power of 0·8. The target sample size was set at 150 patients (75 patients in both groups), allowing for dropouts. Median progression-free survival was estimated by the Kaplan-Meier method and compared between groups with an unstratified log-rank test. Greenwood's formula was used to calculate 95% CIs. HRs were calculated by unstratified Cox proportional hazard methodology.

In the safety analysis, adverse events were converted to Medical Dictionary for Regulatory Activities (version 14.0) preferred terms, and tabulated by grade. Changes in laboratory test data with time were summarised in tables and graphs.

All patients who received at least one dose of the study treatment were included in the safety analysis population. The modified intention-to-treat population for the efficacy analysis included all patients who received at least one dose of study treatment and had tumour assessment at least once after randomisation. Statistical analyses were done with SAS version 9.2.

The study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-111390.

Role of the funding source

The study was designed and funded by Chugai Pharmaceutical Co Ltd and monitored by a clinical research organisation (Niphix Corp, Tokyo, Japan) who obtained all data and did all initial data analyses; further analysis and interpretation was done by the funder, with

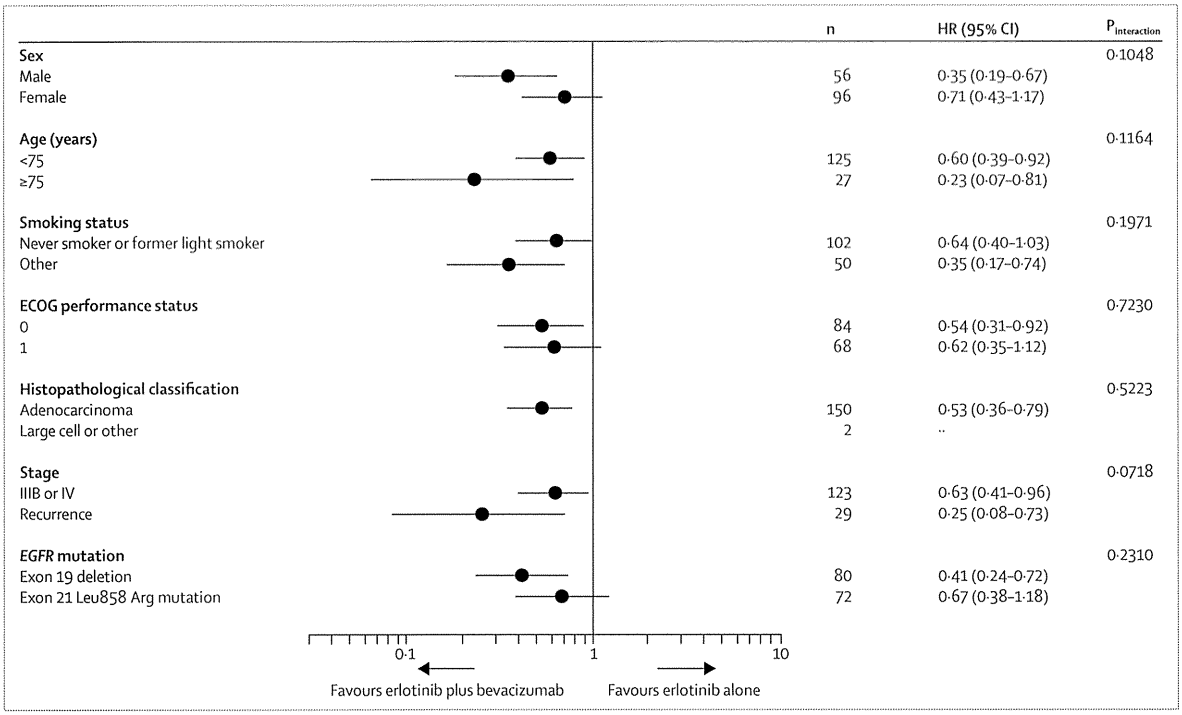

Figure 3: **Forest plot of hazard ratios for progression-free survival by baseline characteristics**
HR=hazard ratio.

	Erlotinib plus bevacizumab group (n=75)	Erlotinib alone group (n=77)
Complete response	3 (4%)	1 (1%)
Partial response	49 (65%)	48 (62%)
Stable disease	22 (29%)	19 (25%)
Progressive disease	0	6 (8%)
Non-evaluable	1 (1%)	3 (4%)

RECIST=Response Evaluation Criteria in Solid Tumors.

Table 2: **Best RECIST response, as determined by independent review committee**

input from the authors and investigators. The initial draft of the report was reviewed and commented on by all authors and by employees of Chugai Pharmaceutical Co Ltd. NobuY had full access to all data, and had final responsibility for the decision to submit the results for publication.

Results

Between Feb 21, 2011, and March 5, 2012, 154 patients were enrolled, of whom 77 were randomly assigned to receive erlotinib plus bevacizumab and 77 to erlotinib alone. Two patients withdrew before treatment started and were excluded (one had multiple thrombosis and the other had increased pleural effusion). Thus, data from 152 patients (75 patients in the erlotinib plus bevacizumab group and 77 in the erlotinib alone group) were included in the analysis population (figure 1). The cutoff date for the primary analysis was June 30, 2013, when 103 progression events had occurred; median follow-up was 20·4 months (IQR 17·4–24·1).

The baseline characteristics of patients were well balanced between the groups (table 1). Median age was 67 years (IQR 60–73), and 27 (18%) patients were aged 75 years or older. *EGFR* mutation subtypes were balanced between the two groups.

Progression-free survival was significantly prolonged with erlotinib plus bevacizumab compared with erlotinib alone (log-rank test p=0·0015; figure 2). When subgroup analyses were done by baseline clinical characteristics, most patient subgroups seemed to have greater benefit from erlotinib plus bevacizumab compared with erlotinib alone. No significant difference was noted between any of the subgroups ($p_{interaction}$>0·05 for all subgroups; figure 3).

Analysis of progression-free survival by mutation subtype showed that in patients whose tumours had an exon 19 deletion (40 [53%] of 75 patients in the erlotinib plus bevacizumab group and 40 [52%] of 77 patients in the erlotinib alone group), median progression-free survival was significantly longer with erlotinib plus bevacizumab than with erlotinib alone (18·0 months [95% CI 14·1–20·6] *vs* 10·3 months [95% CI 8·0–13·1]; HR 0·41 [95% CI 0·24–0·72]; p=0·0011; appendix p 1). In patients whose tumours harboured the Leu858Arg mutation (35 [47%] patients in the erlotinib plus bevacizumab group; 37 [48%] patients in the erlotinib alone group), median progression-free survival was numerically longer with erlotinib plus bevacizumab than with erlotinib alone, but

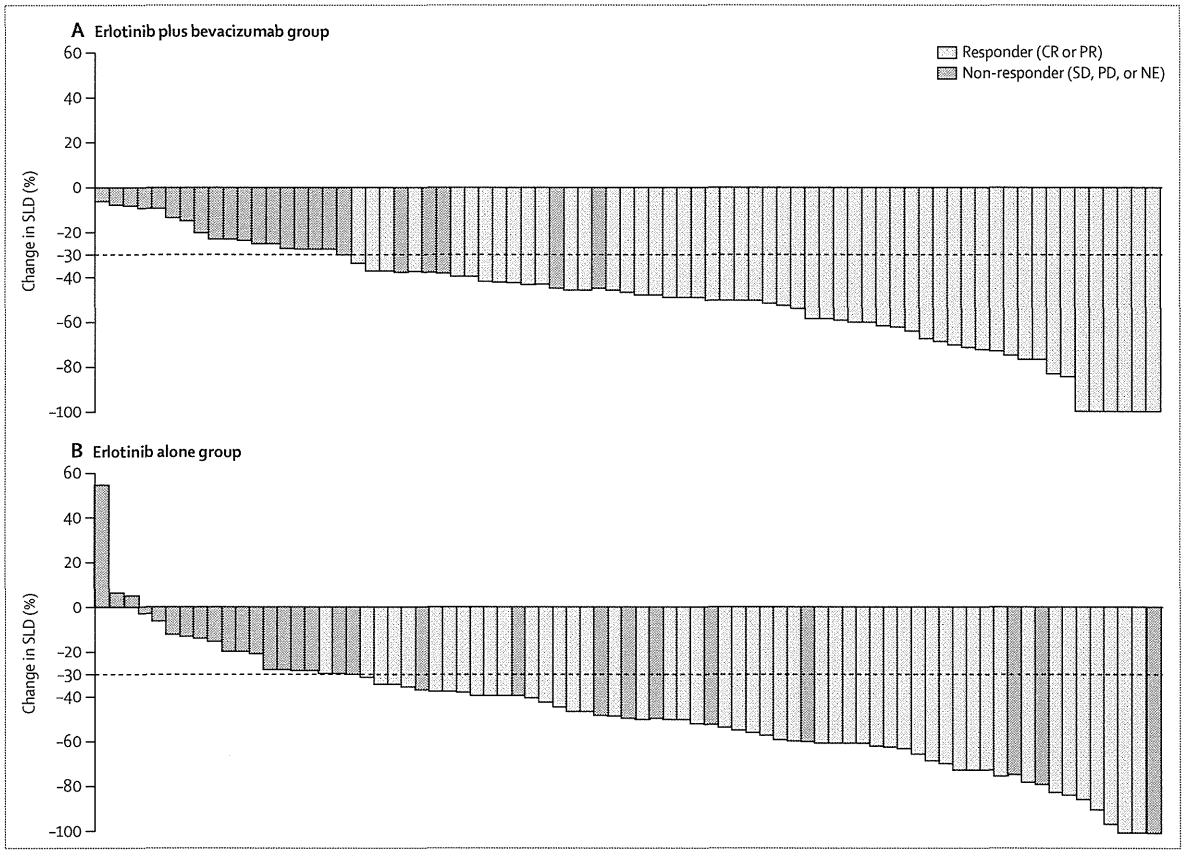

Figure 4: **Waterfall plot of best percentage change from baseline in the sum of longest tumour diameters**
Responders were confirmed by Response Evaluation Criteria in Solid Tumors. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. NE=non-evaluable. SLD=sum of longest diameters.

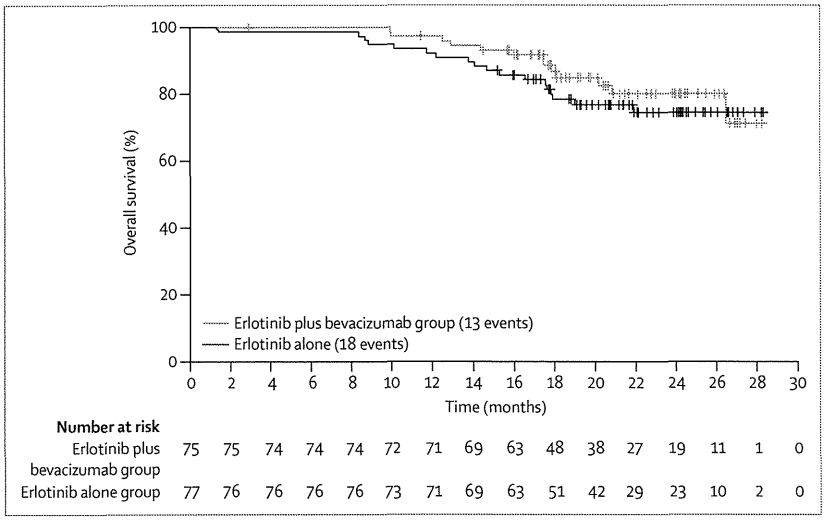

Figure 5: **Overall survival, as determined by independent review committee, in the modified intention-to-treat population**

the difference was not significant (13·9 months [95% CI 11·2–20·9] *vs* 7·1 months [95% CI 4·3–15·2], respectively; HR 0·67 [95% CI 0·38–1·18]; p=0·1653; appendix p 2).

52 (69% [95% CI 58–80]) patients in the erlotinib plus bevacizumab group had an objective response, as did 49 (64% [52–74]) patients in the erlotinib alone group (p=0·4951), although median duration of response was not significantly longer with erlotinib plus bevacizumab than with erlotinib alone (13·3 months [95% CI 11·6–16·5] *vs* 9·3 months [6·9–13·8]; p=0·1118). A greater proportion of patients achieved disease control with erlotinib plus bevacizumab (74 [99%] *vs* 68 [88%]; p=0·0177). Best responses to treatment are shown in table 2.

Figure 4 shows change in tumour size from baseline in the two groups. All patients in the erlotinib plus bevacizumab achieved tumour reduction, but three patients in the erlotinib alone group did not. Of patients who had a 30% or greater reduction in tumour size during treatment, six (8%) patients in the erlotinib plus bevacizumab group and 12 (16%) patients in the erlotinib alone group did not meet the criteria for complete or partial response according to RECIST.

Overall survival data are immature at present and so we cannot present any statistical analyses. At data cutoff, only 13 events (17%) had occurred in the erlotinib plus bevacizumab group and 18 events (23%) in the erlotinib alone group (figure 5).

	Erlotinib plus bevacizumab group (n=75)					Erlotinib alone group (n=77)				
	All	Grade 1–2	Grade 3	Grade 4	Grade 5	All	Grade 1–2	Grade 3	Grade 4	Grade 5
Rash	74 (99%)	55 (73%)	19 (25%)	0	0	76 (99%)	61 (79%)	15 (19%)	0	0
Diarrhoea	61 (81%)	60 (80%)	1 (1%)	0	0	60 (78%)	59 (77%)	1 (1%)	0	0
Paronychia	57 (76%)	55 (73%)	2 (3%)	0	0	50 (65%)	47 (61%)	3 (4%)	0	0
Dry skin	56 (75%)	54 (72%)	2 (3%)	0	0	45 (58%)	45 (58%)	0	0	0
Stomatitis	47 (63%)	46 (61%)	1 (1%)	0	0	46 (60%)	44 (57%)	2 (3%)	0	0
Haemorrhagic event	54 (72%)	52 (69%)	2 (3%)	0	0	22 (29%)	22 (29%)	0	0	0
Liver function disorder or abnormal hepatic function	33 (44%)	27 (36%)	5 (7%)	1 (1%)	0	39 (51%)	25 (32%)	7 (9%)	7 (9%)	0
Hypertension	57 (76%)	12 (16%)	45 (60%)	0	0	10 (13%)	2 (3%)	8 (10%)	0	0
Pruritus	34 (45%)	33 (44%)	1 (1%)	0	0	32 (42%)	32 (42%)	0	0	0
Weight decreased	33 (44%)	33 (44%)	0	0	0	19 (25%)	19 (25%)	0	0	0
Decreased appetite	26 (35%)	25 (33%)	1 (1%)	0	0	26 (34%)	25 (32%)	1 (1%)	0	0
Proteinuria	39 (52%)	33 (44%)	6 (8%)	0	0	3 (4%)	3 (4%)	0	0	0
Dysgeusia	20 (27%)	20 (27%)	0	0	0	17 (22%)	17 (22%)	0	0	0
Nasopharyngitis	20 (27%)	20 (27%)	0	0	0	15 (19%)	15 (19%)	0	0	0
Constipation	17 (23%)	17 (23%)	0	0	0	15 (19%)	14 (18%)	1 (1%)	0	0
Alopecia	13 (17%)	13 (17%)	0	0	0	14 (18%)	14 (18%)	0	0	0
Nausea	12 (16%)	12 (16%)	0	0	0	15 (19%)	15 (19%)	0	0	0
Vomiting	14 (19%)	14 (19%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Malaise	10 (13%)	10 (13%)	0	0	0	10 (13%)	10 (13%)	0	0	0
Insomnia	8 (11%)	8 (11%)	0	0	0	8 (10%)	8 (10%)	0	0	0
Pyrexia	7 (9%)	7 (9%)	0	0	0	9 (12%)	9 (12%)	0	0	0
Upper respiratory tract infection	9 (12%)	9 (12%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Conjunctivitis	8 (11%)	8 (11%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Peripheral oedema	8 (11%)	8 (11%)	0	0	0	6 (8%)	6 (8%)	0	0	0
Fatigue	10 (13%)	9 (12%)	1 (1%)	0	0	3 (4%)	3 (4%)	0	0	0
Nail disorder	9 (12%)	9 (12%)	0	0	0	4 (5%)	4 (5%)	0	0	0
Dry eye	8 (11%)	8 (11%)	0	0	0	3 (4%)	3 (4%)	0	0	0
Dysphonia	8 (11%)	8 (11%)	0	0	0	1 (1%)	1 (1%)	0	0	0

Data are n (%).

Table 3: **Adverse events reported by 10% or more patients for grades 1 and 2 and all adverse events for grades 3–5 (safety population)**

68 (91%) patients in the erlotinib plus bevacizumab group and 41 (53%) patients in the erlotinib group had grade 3 or 4 adverse events. The most common adverse events of any grade in the erlotinib plus bevacizumab group were rash, diarrhoea, hypertension, and paronychia, and in the erlotininb alone group were rash, diarrhoea, and paronychia (table 3). The most common grade 3 or worse adverse events in the erlotinib plus bevacizumab group were hypertension, rash, proteinuria, and liver function disorder or abnormal hepatic function, and in the erlotinib group were rash, liver function disorder or abnormal hepatic function, and hypertension (table 3). Substantially higher (>40%) incidences of hypertension, haemorrhagic events, and proteinuria were noted in the erlotinib plus bevacizumab group compared with the erlotinib alone group (table 3). Serious adverse events were reported by 18 (24%) patients in the erlotinib plus bevacizumab group and 19 (25%) patients in the erlotinib group.

12 (16%) patients in the erlotinib plus bevacizumab group and 14 (18%) patients in the erlotinib group discontinued erlotinib because of adverse events. 31 (41%) patients discontinued bevacizumab because of adverse events (figure 1). Ten patients discontinued both erlotinib and bevacizumab because of adverse events in the erlotinib plus bevacizumab group. Of these patients, seven discontinued erlotinib and bevacizumab simultaneously because of adverse events (liver function disorder or abnormal hepatic function in two patients, and infection, pancreatic cancer, rash, interstitial lung disease, and cerebral infarction in one patient each). In the remaining three patients, bevacizumab was initially discontinued, and patients continued on erlotinib monotherapy, although this was also subsequently discontinued. The dose of erlotinib was reduced to 100 mg for 34 (45%) of 75 patients in the erlotinib plus bevacizumab group and 33 (43%) of 77 patients in the erlotinib alone group; and to 50 mg for 17 (23%) of patients in the erlotinib plus bevacizumab group and eight (10%) patients in the erlotinib alone group.

The major adverse events leading to discontinuation of erlotinib in both groups were liver function disorder or abnormal hepatic function (two [3%] patients in the erlotinib plus bevacizumab group, eight [10%] in the

Panel: Research in context

Systematic review

We searched PubMed for articles published in English until Feb 1, 2014 (with no restrictions for the starting date), using the search terms "bevacizumab", "erlotinib", "NSCLC", and "EGFR". We identified two studies that had assessed the efficacy of erlotinib plus bevacizumab in the first-line setting.[19,20] However, no previous study had assessed the efficacy of the combination of erlotinib and bevacizumab as first-line therapy for patients with activating *EGFR* mutation-positive NSCLC.

Interpretation

To our knowledge, this study is the first to show that the combination of erlotinib and bevacizumab can significantly prolong progression-free survival compared with erlotinib alone in patients with non-squamous *EGFR* mutation-positive NSCLC. Some degree of increased toxicity, particularly hypertension, proteinuria, and haemorrhagic events, was noted with the addition of bevacizumab. Our findings suggest that the combination of erlotinib and bevacizumab could be a new first-line regimen in *EGFR* mutation-positive NSCLC. Two clinical trials, BELIEF (NCT01562028) and ACCRU RC1126 (NCT01532089) are ongoing and the results are awaited to confirm the efficacy and safety shown in our study.

erlotinib alone group), interstitial lung disease (two [3%], three [4%]), and rash (two [3%], none). Major adverse events leading to discontinuation of bevacizumab were proteinuria (11 [15%] patients), haemorrhagic events (nine [12%]), and hypertension (two [3%]). Most haemorrhagic events were low-grade epistaxis or haemorrhoidal bleeding. All of the 11 patients who discontinued bevacizumab because of proteinuria had grade 3 or lower events, and five of these patients recovered during the study period. All of the nine patients who discontinued because of haemorrhagic events had grade 3 or lower events; eight patients improved or recovered during the study period.

The median duration of erlotinib treatment was 431 days (range 21–837) in the erlotinib plus bevacizumab group and 254 days (18–829) in the erlotinib group, whereas median duration of bevacizumab was 325 days (1–815). The median duration of bevacizumab in patients who discontinued treatment because of proteinuria was 329 days (113–639) and because of haemorrhagic events was 128 days (23–357).

The relative dose intensity of erlotinib (calculated as [totally administered dose / total treatment duration] / 150×100) was similar in both groups (95·3% [range 34·7–100·0] in the erlotinib plus bevacizumab group and 98·7% [33·3–100·0] in the erlotinib alone group), whereas that of bevacizumab (calculated as totally administered dose/planned dose×100) was 93·9% (72·4–99·7).

Haemoptysis was reported in six (8%) patients in the erlotinib plus bevacizumab group (five [7%] patients had grade 1 events and one [1%] had a grade 2 event); one patient (1%) had a grade 1 event in the erlotinib alone group. Interstitial lung disease was reported for five (3%) of all patients. One patient in the erlotinib alone group had grade 3 interstitial lung disease, but all other cases were grade 1 or 2, and all patients recovered. During the study period, one patient in the erlotinib group died by drowning, and a potential association with the study drug was confirmed.

No significant difference was noted between the two groups in terms of quality of life, including total FACT-L score, trial outcome index score, and all other subscores, since the standard deviations at each time point overlapped (appendix pp 3–9).

Discussion

In this study, the addition of bevacizumab to erlotinib significantly prolonged progression-free survival in patients with NSCLC with activating *EGFR* mutation-positive disease compared with erlotinib alone. To our knowledge, this is the first randomised study to show a clinically significant treatment effect of combining an EGFR tyrosine-kinase inhibitor with another biological drug in patients with activating *EGFR* mutation-positive NSCLC (panel). We noted clear separation of the Kaplan-Meier survival curves from the start of treatment, despite the use of erlotinib in both groups.

Multivariate analysis according to baseline patient characteristics showed a consistent treatment benefit, with longer progression-free survival noted with erlotinib plus bevacizumab across most subgroups of patients. Previous studies have reported that erlotinib tends to be more effective in tumours with *EGFR* exon 19 deletions versus those with Leu858Arg mutations,[7,8,21] which is consistent with our results.

No new safety signals were identified and the incidence of adverse events (any grade) and serious adverse events was similar between the two groups. There were more grade 3 or worse adverse events in the erlotinib plus bevacizumab group. Discontinuation of bevacizumab because of adverse events was more common than that reported in previous studies.[13,14] One possible reason for this discrepancy could be the longer duration of treatment than in previous studies: the median treatment duration of bevacizumab was 325 days (16 cycles), which is substantially longer than that in previous studies. Furthermore, proteinuria was one of the major adverse events that led to discontinuation of bevacizumab, and the time to onset of bevacizumab discontinuation because of proteinuria tended to be in the later treatment phase (median 329 days [range 113–639]). Nevertheless, despite the high incidence of bevacizumab discontinuation because of adverse events, most of these events (mainly proteinuria and haemorrhagic events) were deemed non-serious and reversible.

The incidence of grade 3 or greater hypertension and proteinuria were higher than those in previous studies, again possibly related to the prolonged duration of treatment. Another potential factor that could explain the difference in the incidence of hypertension is in the definition of grading used; we used CTC-AE version 4.03, whereas previous studies[14,16] used CTC-AE version 3. Akhtar and colleagues[22] showed that the change in CTC-AE version from 3 to 4 could lead to a significant

shift in the severity of adverse events in clinical trials. Furthermore, despite the somewhat higher incidence of hypertension observed in this study, only two (3%) of 75 patients discontinued bevacizumab administration because of hypertension.

Although we noted no significant difference in the proportion of patients achieving an objective response between the erlotinib plus bevacizumab group and erlotinib alone groups, all patients in the erlotinib plus bevacizumab group had a reduction in tumour size. Of those patients who had a greater than 30% reduction in the sum of longest diameter of their target lesions from baseline, more patients in the erlotinib alone group failed to meet the criteria for complete or partial response. These findings suggest that the addition of bevacizumab to erlotinib might help to maintain the tumour-suppressing effect after reduction in tumour size, which might explain the difference in progression-free survival between the two groups.

One possible mechanism to explain this effect could be improved drug delivery. Bevacizumab changes tumour vessel physiology, resulting in increased intratumoral uptake of drugs.[23,24] The results of a preclinical study suggested that patients on lower doses of EGFR tyrosine-kinase inhibitors tend to develop treatment resistance earlier than those who receive higher doses.[25,26] Therefore, achieving a higher intratumoral concentration of erlotinib could delay the appearance of resistant cells. Another possible mechanism that could explain these findings is the effective blocking of angiogenesis signalling via the VEGF receptor and EGFR signalling pathways, which is thought to promote tumour growth.[27,28] In addition to synergistic inhibition of tumour growth signalling, VEGF signal inhibition is still effective for tumours harbouring EGFR tyrosine-kinase inhibitor resistance mutations. In preclinical studies, blocking the VEGF receptor signalling pathway overcame resistance for EGFR signalling blockage by Thr790Met EGFR mutation in vivo.[29,30]

Another treatment strategy that has been recently investigated is the combination of an EGFR tyrosine-kinase inhibitor with chemotherapy. Wu and colleagues[31] reported that platinum doublet chemotherapy with intercalated erlotinib increased progression-free survival compared with platinum doublet chemotherapy alone. In a subset analysis of the *EGFR* mutation-positive population in this study, progression-free survival was 16·8 months. In our study, median progression-free survival with erlotinib and bevacizumab was 16·0 months. The first-line use of erlotinib and bevacizumab could allow chemotherapy to be reserved for subsequent lines of treatment, which might further improve survival outcomes in these patients.

Our study has several limitations. First, the analysis of *EGFR* mutations was not done at a central laboratory and various methods were used, including the peptide nucleic acid, locked nucleic acid PCR clamp method, the PCR invader method, and the cycleave method. However, on the basis of previous evidence, these methods are generally judged to provide consistent results.[32] Second, because some patients are still receiving the first-line treatment and overall survival data are still immature, assessment of subsequent treatment effects after progression is not possible. Data relating to post-study treatment will be reported in due course with updated overall survival results. Third, we did not use the EQ-5D questionnaire developed by the EuroQol group for quality-of-life assessment. Therefore, we could not formally estimate quality-adjusted life-years for a cost-effectiveness analysis. The health economics related to the combined use of erlotinib and bevacizumab remains unclear and should be discussed in future studies. Additionally, follow-up for overall survival is still ongoing and these results are needed before the clinical value of this combination can be determined.

In summary, our study provides, to the best of our knowledge, the first evidence that the addition of bevacizumab to erlotinib confers a significant improvement in progression-free survival when used as first-line treatment for patients with non-squamous NSCLC with activating *EGFR* mutation-positive disease. Some degree of increased toxicity, particularly hypertension, proteinuria, and haemorrhagic events, seems to be associated with the addition of bevacizumab. Our findings suggest that the combination of erlotinib and bevacizumab could be a new first-line regimen in *EGFR* mutation-positive NSCLC, and that further investigation of the regimen is warranted. Two clinical trials, BELIEF (NCT01562028) and ACCRU RC1126 (NCT01532089), are ongoing and the results are awaited to confirm the efficacy and safety shown in our study.

Contributors

NobuY was the principal investigator. TS, TK, MN, KG, NoboY, IO, TY, KT, RH, MF, and NobuY contributed to the study design and data analysis and data interpretation. TS, TK, MN, KG, SA, YH, NoboY, TH, MM, KN, SN, IO, and NobuY contributed to patient recruitment and data collection. NobuY, TS, KT, and RH prepared the initial draft of the report input from other authors. All authors approved the final version of the report.

Declaration of interests

TS received research grants and honoraria from Chugai Pharmaceutical. TK received research grants and honoraria from Chugai Pharmaceutical; honoraria from Eli Lilly, Ono Pharmaceutical, Novartis Pharma, Taiho Pharmaceutical, and AstraZeneca; and research grants from Nippon Boehringer Ingelheim, Kyowa Hakko Kirin, Pfizer, and Shionogi. MN received research grants and honoraria from Chugai Pharmaceutical, Pfizer, Novartis Pharma, Taiho Pharmaceutical, Nippon Boehringer Ingelheim, and AstraZeneca; research grants from MSD and Bristol-Myers Squibb. KG received research grants and honoraria from Chugai Pharmaceutical, Taiho Pharmaceutical and Nippon Boehringer Ingelheim; honoraria from AstraZeneca, Sanofi, Novartis Pharma, Pfizer, Yakult Honsha, Ono Pharmaceutical and Eli Lilly. SA received honoraria from Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, Sawai Pharmaceutical, and Novartis Pharma. YH received research grants and honoraria from Chugai Pharmaceutical, Ono Pharmaceutical, and Taiho Pharmaceutical; honoraria from AstraZeneca, Eli Lilly, Novartis Pharma, and Takeda Pharmaceutical; research grants form Yakult Honsha, MSD, Kyowa Hakko Kirin, and Daiichi Sankyo. NoboY received research grants form Chugai Pharmaceutical, Pfizer, Takeda Bio, Astellas Pharma, Taiho Pharmaceutical, and Bristol-Myers Squibb. TH received research grants form Chugai Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Pfizer, Eli Lilly, Takeda Bio, Novartis Pharma, Ono Pharmaceutical, Daiichi Sankyo, Merck Serono, Kyowa Hakko Kirin, Dainippon Sumitomo Pharma, Bristol-Myers Squibb, and Esai.

MM received honoraria from Chugai Pharmaceutical and AstraZeneca; research grants and honoraria from Nippon Boehringer Ingelheim. KN received honoraria from Chugai Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, and Eli Lilly. SN declares no competing interests. IO received honoraria from Chugai Pharmaceutical, Eli Lilly, Pfizer, and Taiho Pharmaceutical. TY received honoraria from Chugai Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, and Bristol-Myers Squibb. KT and RH are employees of Chugai Pharmaceutical. MF received honoraria from Chugai Pharmaceutical. NobuY received honoraria from Chugai Pharmaceutical, Nippon Boehringer Ingelheim, and AstraZeneca.

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Phase II clinical trial of S-1 plus oral leucovorin in previously treated patients with non-small-cell lung cancer☆

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ABSTRACT

Background: S-1, a novel oral fluoropyrimidine, has potent antitumor activity against non-small-cell lung cancer (NSCLC). Meanwhile, leucovorin enhances the efficacy of 5-fluorouracil by inhibiting thymidylate synthase. Therefore, this phase II clinical trial evaluated the safety and efficacy of S-1 plus leucovorin combination therapy for previously treated patients with NSCLC.
Patients and methods: Patients with stage IIIB or IV NSCLC were prospectively enrolled if they received 1 or 2 prior chemotherapy regimens. S-1 (40–60 mg) and leucovorin (25 mg) were administered together orally twice per day for 7 consecutive days followed by 7 days of rest. This 2-week cycle was repeated for a maximum of 25 cycles until the onset of disease progression or unacceptable adverse events. Endpoints included objective tumor response, progression-free survival, overall survival, and safety.
Results: Among 33 patients, 6 (18.2%), 14 (42.4%), and 11 (33.3%) had partial response, stable disease, and progressive disease, respectively. Median progression-free and overall survival times were 3.5 and 11.7 months, respectively. The common grade 3 toxicities included stomatitis (18.2%), anorexia (12.1%), and neutropenia (9.1%). One patient had pneumatosis cystoides intestinalis, and another experienced paralytic ileus. There were no treatment-related deaths.
Conclusions: S-1 plus leucovorin combination therapy demonstrated promising efficacy and an acceptable toxicity profile in previously treated patients with NSCLC.

1. Introduction

Lung cancer is one of the leading causes of death worldwide [1]. Approximately 80% of lung cancers result from non-small-cell histology, and most patients present with locally advanced stage III or metastatic stage IV disease at diagnosis. Advanced non-small-cell lung cancer (NSCLC) generally results in poor outcomes, except for a small patient population with specific genetic alterations conferring susceptibility to specific molecular targeted treatments [2]. The results of phase III trials for previously treated patients with NSCLC indicate that single-agent chemotherapy with docetaxel, pemetrexed, or erlotinib as the standard chemotherapy regimen for recurrent NSCLC results in a response rate of 8.8–9.1%, median survival time of 6.7–8.3 months, and 1-year survival rate of 30–31% [3,4]. S-1 (Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) is a capsule preparation comprising tegafur, an oral 5-fluorouracil (5-FU) pro-drug, 5-chloro-2,4-dihydroxypyridine (CDHP), and oteracil potassium at a molar ratio of 1.0:0.4:1.0. CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase, an enzyme for 5-FU degradation. Meanwhile, oteracil potassium is a reversible competitive inhibitor of orotate phosphoribosyl transferase, an enzyme for 5-FU phosphoribosylation in the gastrointestinal mucosa [5]. The antitumor activity of S-1 against

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NSCLC has been proven in several clinical trials. First-line treatment of S-1 combined with platinum showed favorable outcomes in 2 phase III trials for metastatic NSCLC [6,7]. Chemoradiation with S-1 plus cisplatin also showed promising results in locally advanced NSCLC [8,9]. In second- or third-line settings, several phase II trials demonstrate promising antitumor activity of S-1 monotherapy for previously treated patients with advanced NSCLC [10–13]. The addition of leucovorin increases the intracellular concentration of reduced folates, thus stabilizing the 5-fluorodeoxyuridine monophosphate/thymidylate synthase enzyme complex, providing the biochemical rationale for adding leucovorin to 5-FU and tegafur chemotherapy regimens [14,15]. An in vivo study of S-1 plus leucovorin treatment using xenograft mouse models of human colorectal cancer cells demonstrated that leucovorin might improve the antitumor activity of S-1 [16]. A phase II clinical trial of S-1 plus oral leucovorin for chemotherapy-naïve patients with metastatic colorectal cancer recently demonstrated promising efficacy [17]. In addition, this treatment might improve the convenience of cancer care because of the combination of oral medicines. Accordingly, the present phase II study evaluated the safety and efficacy of S-1 plus leucovorin combination therapy in previously treated patients with advanced NSCLC.

2. Methods

2.1. Patients

This was an open-labeled, multicenter, single-arm, phase II study. Patients were enrolled from the following 5 institutions: Kinki University, the National Cancer Center Hospital East, the National Kyushu Cancer Center, Osaka City General Hospital, and the Shizuoka Cancer Center. The eligibility criteria were as follows: (1) histologically and/or cytologically proven stage IIIB or IV NSCLC with at least 1 measurable lesion; (2) 1 or 2 previous cytotoxic chemotherapy regimens; *EGFR* tyrosine kinase inhibitors and adjuvant chemotherapy were not counted as a prior treatment; and (3) Eastern Cooperative Oncology Group performance status 0–1 and adequate organ function. Patients were excluded if they had received systemic chemotherapy or thoracic radiation within the previous 4 weeks, radiation to extrathoracic lesions within the previous 2 weeks, or previous treatment with fluoropyrimidine agents. Patients with serious medical conditions including other malignancies, symptomatic brain metastases, psychiatric disorders, active infectious diseases, and active ischemic heart disease were also excluded. A data and safety monitoring board monitored the trial on an ongoing basis. The protocol, protocol amendments, informed consent, and other documents pertaining to the study were approved by the institutional review board of each participating center. The first and last authors vouch for the accuracy and completeness of the data and analyses reported as well as the fidelity of the report to the study protocol. This trial is registered on the clinical trials site of the University Hospital Medical Information Network Clinical Trials Registry in Japan (registration number: UMIN000004568).

2.2. Treatment plan

The dose of S-1 (capsules containing tegafur 20 or 25 mg) was determined according to body surface area as follows: 40, 50, and 60 mg for <1.25, 1.25–1.50, and ≥1.50 m^2, respectively.

Leucovorin (25-mg tablets) was administered at a fixed dose of 25 mg. S-1 and leucovorin were administered together orally twice per day for 7 consecutive days followed by 7 days of rest; this 2-week cycle was repeated for a maximum of 25 cycles until the onset of disease progression or unacceptable adverse events.

Table 1
Patient characteristics.

Characteristics	$N = 33$	%
Gender (male:female)	25:8	
Age, median (range)	65 (27–74)	
ECOG-PS 0	13	39.4
1	20	60.6
Histology		
Adenocarcinoma	26	78.8
Squamous cell carcinoma	4	12.1
Large cell carcinoma	2	6.1
Pleomorphic carcinoma	1	3.0
Stage		
IIIB	5	15.2
IV	28	84.8
No. of prior chemotherapy		
1 Regimen	11	33.3
2 Regimens	19	57.6
3 Regimens	3	9.1

The dose of S-1 could be decreased by 2 levels to a minimum dose of 20 mg twice daily in the event of following toxicities: grade 4 neutropenia or non-hematologic toxicity, or grade 3 thrombocytopenia, diarrhea, stomatitis, or skin rash. The dose of leucovorin was not decreased.

2.3. Study assessment

Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1, and computed tomography scans were performed every 4–6 weeks. If a patient responded, response was confirmed through tumor assessments at least 4 weeks after the first documentation of a response. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Physical examination, chest radiograph, laboratory chemistry, and hematology were performed at baseline and on day 1 of each cycle.

2.4. Statistical analysis

The primary endpoint of the study was the antitumor activity of S-1 plus leucovorin assessed according to the overall response rate (ORR) including complete response (CR) and partial response (PR). The secondary endpoints were overall survival (OS), progression-free survival (PFS), and safety profile. We defined acceptable and unacceptable ORRs as 20% and 5%, respectively. The sample size was determined to be 30 on the basis of the exact binomial probability distribution of Southwest Oncology Group 2-stage design with a statistical power $(1 - \beta)$ of 80% and significance level (α) of 5%. All analyses were performed using JMP version 9.0 for Windows (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

From December 2010 through September 2011, a total of 33 patients (median age: 65 years, range: 27–74 years) who met the inclusion criteria were enrolled (Table 1). The majority of the patients had stage IV disease (28 patients, 84.8%), including 5 patients (15.2%) with postoperative relapse. Histopathological diagnoses included adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, and pleomorphic carcinoma in 26, 4, 2, and 1 patient, respectively. An activating *EGFR* gene mutation was assessed in 26 patients, 5 of whom had a mutant gene. Regarding prior chemotherapy, 1 patient had received platinum-based chemoradiotherapy, and 2 patients had received gefitinib

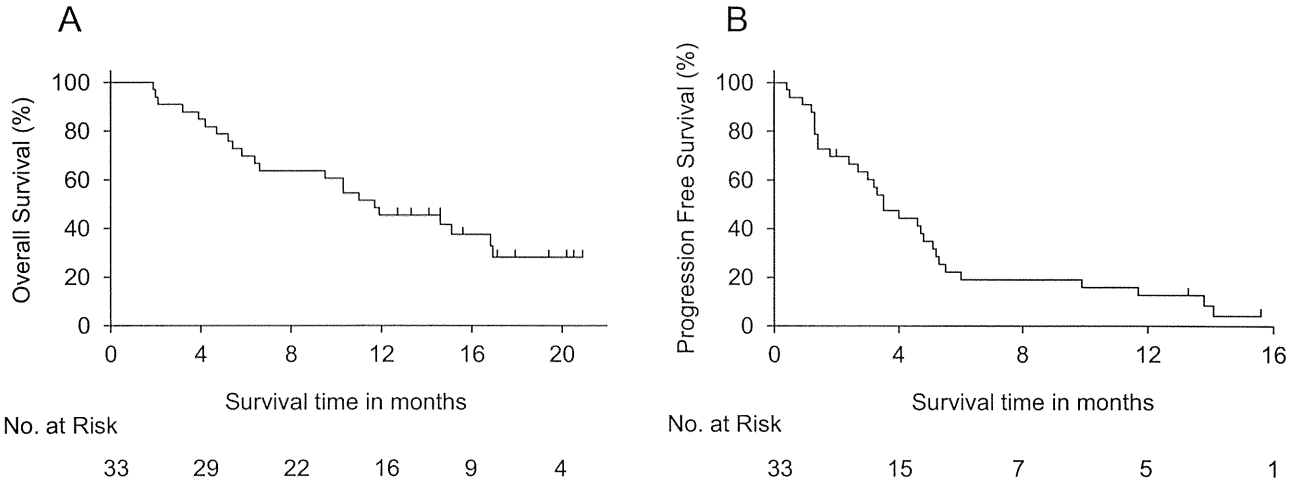

Fig. 1. (A) Kaplan Meier survival curve of overall survival and (B) Kaplan Meier survival curve of progression free survival.

as a first-line treatment. The remaining 30 patients had received platinum-based chemotherapy with or without bevacizumab as a first-line treatment. A total of 23 patients had received second-line or more chemotherapy before study entry.

3.2. Treatment delivery

A total of 255 treatment cycles were administered to patients. The median number of treatment courses was 6 (range: 1–25). The median treatment period was 2.5 months (95% confidential interval [CI]: 1.1–4.0 months). Dose reduction and treatment interruption were required in 13 (39.4%) and 6 (18.2%) patients, respectively. The reasons for treatment withdrawal were disease progression in 22 (66.7%), toxicities in 4 (12.1%), protocol completion in 3 (9.1%), and patient preference in 4 (12.1%). The median total doses per 6 weeks for S-1 and leucovorin were 2100 mg (range: 840–2520 mg) and 1050 mg (range: 350–1050 mg), respectively. The median relative dose intensity for the first 6 weeks for S-1 and leucovorin were 82.5% (95% CI: 74.8–90.3%) and 84.5% (95% CI: 76.8–92.2%), respectively.

3.3. Efficacy

The objective tumor response (the primary endpoint) was assessed by independent evaluators in all 33 patients. One woman was considered unevaluable for tumor response because she asked to discontinue the study treatment after 1 course because of grade 1 mucositis and declined radiological assessment. Among the remaining 32 patients, 0, 6, 15, and 11 had complete response, partial response, stable disease, and progressive disease, respectively. The response rate was 18.2% (95% CI: 7.0–35.5%), and the disease control rate was 63.6% (95% CI: 45.1–79.6%, Table S1). Although the patients had heterogeneous background characteristics including pathological diagnosis and the number of previous treatments, most patients experienced tumor shrinkage or stabilization during the study period (Fig. S1). All 33 patients were evaluable for the OS and PFS, and their median follow-up duration was 17.9 (95% CI: 14.1–20.2) months. The cutoff date for analysis was November 6, 2012. At the time of analysis, 11 (33.3%), 3 (9.1%), and 0 (0%) patients were alive, free of progression, and on study treatment, respectively. Median survival time was 11.7 months (95% CI: 6.1–16.9 months) and the 1-year survival rate was 45.5% (95% CI: 29.6–62.3%, Fig. 1A). Median PFS was 3.5 months (95% CI: 2.4–5.1 months, Fig. 1B), and the median time to treatment failure was 2.5 months (95% CI: 1.1–4.0 months). A Comparison of efficacy with S-1 monotherapy showed a relatively better efficacy profile in our study treatment (Table 2). A comparison of efficacy among histology types was also summarized in Table S2. A total of 2 out of 26 patients with adenocarcinoma (7.7%) and 4 out of 7 patients with non-adenocarcinoma (57.1%) showed partial response ($p = 0.2233$, Fisher's exact test) including 2 squamous carcinoma, 1 pleomorphic carcinoma, and 1 large cell carcinoma. Median OS was 10.3 in patients with adenocarcinoma and not reached in non-adenocarcinoma ($p = 0.0505$, log-rank test). A total of 19 patients (57.6%) received additional treatments after the study treatment, including docetaxel, erlotinib with or without investigational drugs in clinical trials, gemcitabine, pemetrexed, and palliative radiation therapy in 5, 5, 4, 2, and 3 patients, respectively.

3.4. Safety and adverse events

Safety data from all 33 patients are shown in Table 3. All toxicities with an incidence ≥50% included anemia (93.9%), hypoalbuminemia (87.9%), anorexia (84.8%), stomatitis (72.7%), fatigue (60.6%), pigmentation (57.6%), nausea (54.5%), and leukocytopenia (51.5%). Grade 3 toxicity occurred in 15 patients (45.5%). Grade 3 toxicities with an incidence ≥10% included stomatitis (18.2%) and anorexia (12.1%). One patient each had pneumatosis cystoides intestinalis (grade 3) and paralytic ileus (grade 3); both toxicities improved as a result of interrupting treatment and subsequently resuming treatment with a reduced dose. There were no grade 4 toxicities, febrile neutropenia, or interstitial lung disease. The dose was reduced at least once in 13 patients (39.4%), mainly because of stomatitis and anorexia. Rest periods were prolonged in 15 patients (45.5%), mainly because of persistent stomatitis, anorexia, and fatigue. The median number of treatment courses until the worst grade of stomatitis, anorexia, fatigue, diarrhea, and rash was 2, 1, 3, 2, and 1, respectively. There were no treatment-related deaths. A Comparison of ≥grade 3 adverse events with S-1 monotherapy showed increased percentage of anorexia, stomatitis, and neutropenia in our study treatment (Table 3).

4. Discussion

This multicenter phase II clinical trial demonstrates the efficacy and safety of S-1 plus oral leucovorin combination therapy for previously treated patients with NSCLC. The results show that the treatment has promising antitumor activity, with an objective response rate of 18.2%, which meets the primary endpoint of this

Table 2
Comparison of efficacy with S-1 monotherapy.

Efficacy	Our study	Totani et al. [12]	Shiroyama et al. [11]	Govindan et al. [10]	Wada et al. [13]
N	33	48	44	57	30
Treatment line	2nd or 3rd	2nd	2nd	2nd	≥2nd
Response rate (%)	18.2	12.5	13.6	7.1	26.7
Disease control rate (%)	63.6	39.6	77.3	55.3	70.0
Median PFS (months)	3.5	2.5	4.2	2.9	3.1
Median OS (months)	11.7	8.2	16.4	7.3	11.2
1-year survival rate (%)	45.5	29.6	60.3	31.6	43.3

PFS, progression-free survival; OS, overall survival.

study. The treatment was safe and tolerable for all patients, and there were no grade 4 toxicities or treatment-related deaths.

Leucovorin is a biochemical modulator of 5-FU that stabilizes the inhibitory ternary complex formed between thymidylate synthase and the active metabolite of 5-FU, 5-fluorodeoxyuridylate. A meta-analysis of advanced colorectal cancer cases revealed that leucovorin improves response rates and OS when combined with 5-FU in comparison to 5-FU alone [18]. The 5-FU/leucovorin-based regimens such as 5-FU/leucovorin plus oxaliplatin and/or irinotecan are standard treatments for metastatic colorectal cancer [19]. The role of S-1 in the treatment of other solid tumors including gastric, colorectal, biliary tract, pancreatic, and lung cancers has recently been increasing [20–22]. The antitumor activity of S-1 against NSCLC has been proven in several clinical trials [6–8]. There are several reports of S-1 monotherapy as a second-line or subsequent-line treatment for previously treated NSCLC [10–13], with response rates ranging from 7.1% to 26.7%, median PFS from 2.5 to 4.2 months, median survival time from 8.2 to 16.4 months, and the 1-year survival rate from 29.6% to 60.3% (Table 2). Relatively low incidences of severe toxicities (i.e., grade 3 or 4) were reported, and the treatment was considered to be well tolerated.

The present study is the first report of the efficacy and safety of S-1/leucovorin combination therapy for advanced NSCLC. The results revealed a relatively high response rate and long PFS, indicating that leucovorin potentiates the antitumor activity of S-1. However, regarding safety, the incidence of toxicity was higher with S-1/leucovorin combination therapy in the present study than with S-1 monotherapy in previous studies; approximately 45% of the present patients experienced grade 3 toxicities such as stomatitis, anorexia, and neutropenia in comparison to <20% of patients receiving S-1 monotherapy. Similarly, in the clinical trial of S-1/leucovorin combination therapy for colorectal cancer, treatment resulted in a relatively high incidence of non-hematologic toxicities. In the original 4-week regimen, in which S-1/leucovorin was administered for 2 weeks followed by 2 weeks of rest, grade 3 toxicities occurred in 55% of patients, including diarrhea, anorexia, stomatitis, and neutropenia in 32%, 21%, 20%, and 14%, respectively. As a result, 59% of the patients in that study required dose reduction, and 54% required a prolonged rest period [17]. A modified less-toxic treatment schedule in which S-1/leucovorin is administered for 1 week followed by 1 week of rest was recently proposed in a multicenter international phase II study conducted in Japan and China [23]. This regimen resulted in decreased occurrence of severe toxicities associated with this combination therapy without reducing relative dose intensity or efficacy. Grade 3 diarrhea, anorexia, stomatitis, and neutropenia occurred in 8.3%, 2.8%, 8.3%, and 9.7% of patients, respectively. Although we used the latter treatment schedule (i.e., 1 week on/1 week off), the incidences of stomatitis (18.2%) and anorexia (12.1%) were slightly higher. This might be due to the differences in patient characteristics between studies: our patients were administered 1 or more chemotherapeutic regimens, while the other study included

Table 3
Treatment-related adverse events.

Adverse events, *N* (%)[a]	Any grade	Grade 2	Grade 3	Reference[b] ≥Grade 3 in S-1 monotherapy (%)
Non-hematologic				
Anorexia	28(84.8)	15(45.5)	4(12.1)	2.1–7.1
Stomatitis	24(72.7)	10(30.3)	6(18.2)	0.0–3.6
Fatigue	20(60.6)	11(33.3)	1(3.0)	0.0–12.5
Hyperpigmentation	19(57.6)	4(12.1)	–	–
Nausea	18(54.5)	9(27.3)	–	0.0–5.4
Vomiting	12(36.4)	5(15.2)	0(0.0)	0.0–1.8
Diarrhea	15(45.5)	5(15.2)	1(3.0)	0.0–21.4
Constipation	13(39.4)	3(9.1)	0(0.0)	0.0
Skin rash	13(39.4)	5(15.2)	1(3.0)	1.8–2.1
Alopecia	5(15.2)	–	–	–
Hematologic				
Anemia	31(93.9)	14(42.4)	1(3.0)	1.8–4.5
Hypoalbuminemia	29(87.9)	7(21.2)	0(0.0)	0.0
Leukocytopenia	17(51.5)	7(21.2)	2(6.1)	0.0–4.5,
Hyponatremia	14(42.4)	0(0.0)	2(6.1)	0.0
Hypocarcemia	13(39.4)	2(6.1)	0(0.0)	0.0
Neutropenia	10(30.3)	6(18.2)	3(9.1)	2.1–4.5
Thrombocytopenia	9(27.3)	0(0.0)	0(0.0)	0.0
Hypokalemia	6(18.2)	0(0.0)	2(6.1)	0.0
Alkaline phosphatase increased	6(18.2)	2(6.1)	0(0.0)	0.0
Hyperkalemia	6(18.2)	0(0.0)	0(0.0)	0.0
Total bilirubin increased	6(18.2)	0(0.0)	0(0.0)	0.0

[a] No grade 4 or more toxicity was reported.
[b] The data was a summary of Refs. [10–13].

only chemotherapy-naïve colorectal cancer patients. In addition, the median age was higher (65 vs. 60 years) and the percentage of ECOG-PS grade 0 was lower (39.4% vs. 54.9%) in our patients than that in the previous study. However, in the present study, all of the toxicities were easily manageable by routine supportive care with short treatment interruption, and most of the patients were able to resume treatment with or without dose reduction.

A major limitation of this study is a small study population comprising exclusively Japanese patients. Accordingly, the toxicity profile of S-1 is reported to differ by ethnicity [10,24]. The primary dose-limiting toxicity of S-1 in American and European clinical trials was gastrointestinal toxicity including diarrhea and nausea/vomiting [25,26], whereas that in Japanese clinical trials was hematological toxicity [27]. Because S-1/leucovorin combination therapy resulted in a relatively high incidence of gastrointestinal toxicities, caution should be exercised when administering this treatment to patients of different ethnicities, especially American and European populations.

In conclusion, this phase II study demonstrates that S-1 with oral leucovorin combination therapy has promising antitumor activity and is well tolerated in previously treated patients with NSCLC. Nevertheless, further large-scale Phase III clinical trials comparing the efficacy of S-1/leucovorin combination therapy with current standard treatment are required to confirm the benefits of this treatment.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2014.10.010.

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Treatment of Patients with Adult T Cell Leukemia/Lymphoma with Cord Blood Transplantation: A Japanese Nationwide Retrospective Survey

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A B S T R A C T

Allogeneic bone marrow and peripheral blood stem cell transplantations are curative treatment modalities for adult T cell leukemia/lymphoma (ATLL) because of the intrinsic graft-versus-ATLL effect. However, limited information is available regarding whether cord blood transplantation (CBT) induces a curative graft-versus-ATLL effect against aggressive ATLL. To evaluate the effect of CBT against ATLL, we retrospectively analyzed data from 175 patients with ATLL who initially underwent single-unit CBT. The 2-year overall survival (OS) rate was 20.6% (95% confidence interval [CI], 13.8% to 27.4%). A multivariate analysis revealed that the development of graft-versus-host disease (GVHD) was a favorable prognostic factor for OS (hazard ratio, .10; 95% CI, .01 to .94; $P = .044$). Furthermore, the 2-year OS (42.7%; 95% CI, 28.1% to 56.6%) of patients with grade 1 to 2 acute GVHD was higher than that of patients without acute GVHD (24.2%; 95% CI, 11.2% to 39.8%; $P = .048$). However, the cumulative incidence of treatment-related mortality (TRM) was high (46.1%; 95% CI, 38.2% to 53.7%), and early death was particularly problematic. In conclusion, CBT cures patients with ATLL partly through a graft-versus-ATLL effect. However, novel interventions will be required, particularly in the early phase, to reduce TRM and optimize GVHD.

INTRODUCTION

Adult T cell leukemia/lymphoma (ATLL), an aggressive peripheral T cell neoplasm caused by the human T cell lymphotropic/leukemia virus type-1, has an extremely poor prognosis [1]. Intensive chemotherapy and autologous stem cell transplantation have not been shown to improve this prognosis [2,3]. As a curative treatment, allogeneic hematopoietic stem cell transplantation (allo-HSCT) can confer long-term remission via a graft-versus-ATLL effect in a proportion of patients with ATLL [4-7]. Recent reports have demonstrated that allo-HSCT using bone marrow (BM) or peripheral blood stem cells (PBSC) from a related or unrelated donor can effectively treat ATLL, yielding a 3-year overall survival rate

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(OS) of approximately 30% [8-16]. However, patients with ATLL typically lack a suitable HLA-identical sibling donor because both the recipients and donors are typically elderly and because the aggressive ATLL tumor burden reduces the available time to find a suitable unrelated donor within the Japan Marrow Donor Program. Umbilical cord blood, which can serve as an alternative to BM or PBSC as a source of stem cells, has been used primarily to treat children; however, the number of unrelated-donor cord blood transplantation (CBT) procedures used to treat adult patients with ATLL is increasing in Japan. The rapid availability of CBT may provide a great advantage for patients who require urgent allo-HSCT to treat aggressive ATLL [17].

Currently, the outcome of CBT in patients with acute leukemia is comparable to that of other graft sources [18,19]; however, there are few reports on the outcomes of CBT in patients with ATL [20,21]. Moreover, it is difficult to draw firm conclusions regarding the efficacy of this procedure because of the small number of cases. Therefore, to evaluate the role of CBT for ATLL in a larger and more recent cohort, we performed a nationwide retrospective study of patients with ATLL who underwent CBT as the initial allo-HSCT.

PATIENTS AND METHODS

Data Collection

We analyzed nationwide survey data from the Japan Society for Hematopoietic Cell Transplantation regarding patients with ATLL who had undergone an initial CBT between March 2001 and December 2009 (n = 175). This analysis included the patients' clinical characteristics, such as the age at transplantation, gender, disease status at transplantation, date of transplantation, time from diagnosis to transplantation, conditioning regimens, and number of infused cells. The number of mismatches was counted with respect to HLA-A, HLA-B (low-resolution typing), and DRB1 (high-resolution typing). The present study was approved by the data management committees of the Japan Society for Hematopoietic Cell Transplantation as well as the institutional ethics committee of the Kyushu University Graduate School of Medical Sciences.

Definitions

OS was defined as the time from transplantation until death, and patients who remained alive at the time of the last follow-up were censored. The causes of death were reviewed and categorized as either ATLL-related or transplantation-related mortality (TRM). *ATLL-related mortality* was defined as death caused by a relapse or progression of ATLL, whereas *TRM* was defined as any death related to transplantation other than ATLL-related mortality, according to the judgment of each institution. The patients were divided into 2 groups according to the conditioning regimen: full-intensity conditioning (FIC) and reduced-intensity conditioning (RIC). FIC and RIC were defined according to the proposals of Giralt et al. [22] and Bacigalupo et al. [23], respectively, with slight modifications. In the present study, conditioning regimens that included ≥5 Gy of total body irradiation (TBI) in a single fraction or ≥8 Gy of TBI in multiple fractions, oral busulfan (BU) at >8 mg/kg, intravenous BU at >6.4 mg/kg, or melphalan (Mel) at >140 mg/m^2 were considered FIC; all others were classified as RIC.

Statistical Analysis

Descriptive statistics were used to summarize the variables related to patient demographics and transplantation characteristics. The probability of the OS time was estimated according to the Kaplan-Meier method. To evaluate the influences of confounding factors on acute graft-versus-host disease (GVHD) and survival, the log-rank test and proportional hazards modeling were used for the univariate and multivariate analyses, respectively. The Cox proportional hazard model was used for the multivariate analyses of OS in which all independent variables were incorporated in the model, followed by the use of a stepwise selection method [24]. Fine and Gray proportional hazard modeling was used to estimate the effects of the same variables used in the multivariate analysis for OS on the cumulative incidence rates of TRM and ATLL-related mortality [25,26]. In these regression models, the occurrence of GVHD was treated as a time-dependent covariate [27]. In the analysis of acute GVHD, patients were assigned to the "no acute GVHD group" at the time of transplantation and transferred to the "acute GVHD group" at the onset of the maximum grade of acute GVHD. The landmark method was used to evaluate the effects of GVHD on OS and the cumulative incidence of disease-associated and treatment-related deaths among patients who remained alive at 60 days for acute GVHD and at 100 days for chronic GVHD after transplantation. Factors associated with at least borderline significance ($P \leq .10$) in the univariate analysis were subjected to a multivariate analysis using a backward stepwise covariate selection. All P values were 2-tailed, and P values ≤.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) [28].

RESULTS

Patient Characteristics

The characteristics of 175 ATLL patients who received a single CBT are shown in Table 1. The median age at CBT was 55 years (range, 27 to 79 years). The cohort comprised 70 women and 105 men with the following ATLL statuses at CBT: complete remission (CR; n = 50), not in CR (n = 116), and unknown (n = 9). The conditioning regimen intensity was classified as FIC in 63 (36%) patients and RIC in 128 (62%) patients. FIC was further subdivided into 2 groups as follows: TBI (n = 47) or non-TBI (n = 15). RIC was also subdivided into 3 groups as follows: fludarabine (Flu) + Mel (n = 75), Flu + BU (n = 15), and other types (n = 15). Cyclosporine and tacrolimus were administered for prophylaxis to 90 (51%) and 77 patients (44%), respectively. Cyclosporine-based prophylaxis was subdivided into 3 groups as follows: (1) cyclosporine

Table 1
Patient Characteristics at Cord Blood Transplantation

Variables	No. of Patients (n = 175)
Age at transplantation, median (range), yr	55 (27-79)
Gender	
Male	105
Female	70
Disease status at transplantation	
CR	50
Not in CR	116
Unknown	9
Conditioning regimen	
FIC	63
RIC	108
Unknown	4
GVHD prophylaxis	
Cyclosporine-based	90
Tacrolimus-based	77
Unknown	8
Time from diagnosis to transplantation, d	
<200	94
≥200	75
Unknown	6
Year of transplantation	
<2005	71
≥2005	104
HLA matching*	
0 mismatched loci	5
1 mismatched locus	36
2 mismatched loci	73
≥3 mismatched loci	42
Unknown	19
ABO matching	
Matched	56
Minor mismatched	49
Major mismatched	69
Unknown	1
Nucleated cells infused per 10^7/kg, median (range)	2.58 (.36-5.34)
CD34-positive cells infused per 10^5/kg, median (range)	.85 (.07-5.39)

* Number of mismatches was counted among HLA-A, -B (low-resolution typing), and DRB1 (high-resolution typing).

alone (n = 33), (2) cyclosporine + short-term methotrexate (MTX) (n = 45), and (3) cyclosporine + mycophenolate mofetil (MMF; n = 12). Tacrolimus-based prophylaxis was subdivided into 4 groups as follows: (1) tacrolimus alone (n = 37), (2) tacrolimus + short-term MTX (n = 32), (3) tacrolimus + MMF (n = 5), (4) and tacrolimus + prednisolone (n = 3). Ninety-four patients (54%) received CBT < 200 days after diagnosis. One hundred twenty-four (71%) patients underwent CBT with 2 HLA-mismatched loci. The numbers of infused nucleated and CD34-positive cells were 2.58 × 10^7/kg (range, .36 to 5.34 × 10^7/kg) and .85 × 10^5/kg (range, .07 to 5.39 × 10^5/kg), respectively. Engraftment evaluation was possible in 125 patients (71%) within a median interval of 19 days after CBT (range, 7 to 46 days). Among the survivors, the median follow-up duration was 22.5 months (range, 0 to 74.5 months).

Prognostic Factors for Survival

The OS rates of 175 patients with ATLL who received CBT were 30.2% (95% confidence interval [CI], 23.0% to 37.4%) at 1 year and 20.6% (95% CI, 13.8% to 27.4%) at 2 years (Figure 1A). The cumulative incidence rates of ATLL-related mortality and TRM at 2 years were 31.9% (95% CI, 24.8% to 39.3%) and 46.4% (95% CI, 38.5% to 54.0%), respectively (Figure 1B). The following confounding factors affected survival: age, gender, disease status at transplantation, days from diagnosis to transplantation, date of transplantation, age at transplantation, conditioning regimen, number of infused nucleated and CD34-positive cells, ABO compatibility, HLA compatibility, GVHD prophylaxis, and the development of acute GVHD. A univariate analysis revealed that higher OS ($P < .05$) correlated with CR at transplantation, minor ABO incompatibility, the addition of other agents to calcineurin inhibitors (MTX or MMF), and the development of acute GVHD (Table 2). A multivariate analysis was performed to further examine the effects of an age <55 years, the development of acute GVHD as a time-dependent covariate coincident with CR at transplantation, minor ABO incompatibility, and the addition of other agents to calcineurin inhibitors (Table 3). Compared with the absence of GVHD, the development of acute GVHD was associated independently with higher OS (hazard ratio [HR], .10; 95% CI, .01 to 0.94; $P = .044$).

Effects of Acute GVHD on Survival

To further validate the effect of acute GVHD on OS, we examined survival according to the acute GVHD grade in a landmark analysis. The median time to onset of acute GVHD of any grade after transplantation was 21 days (range, 5 to 100 days). Acute GVHD occurred in 80 patients (46%) as

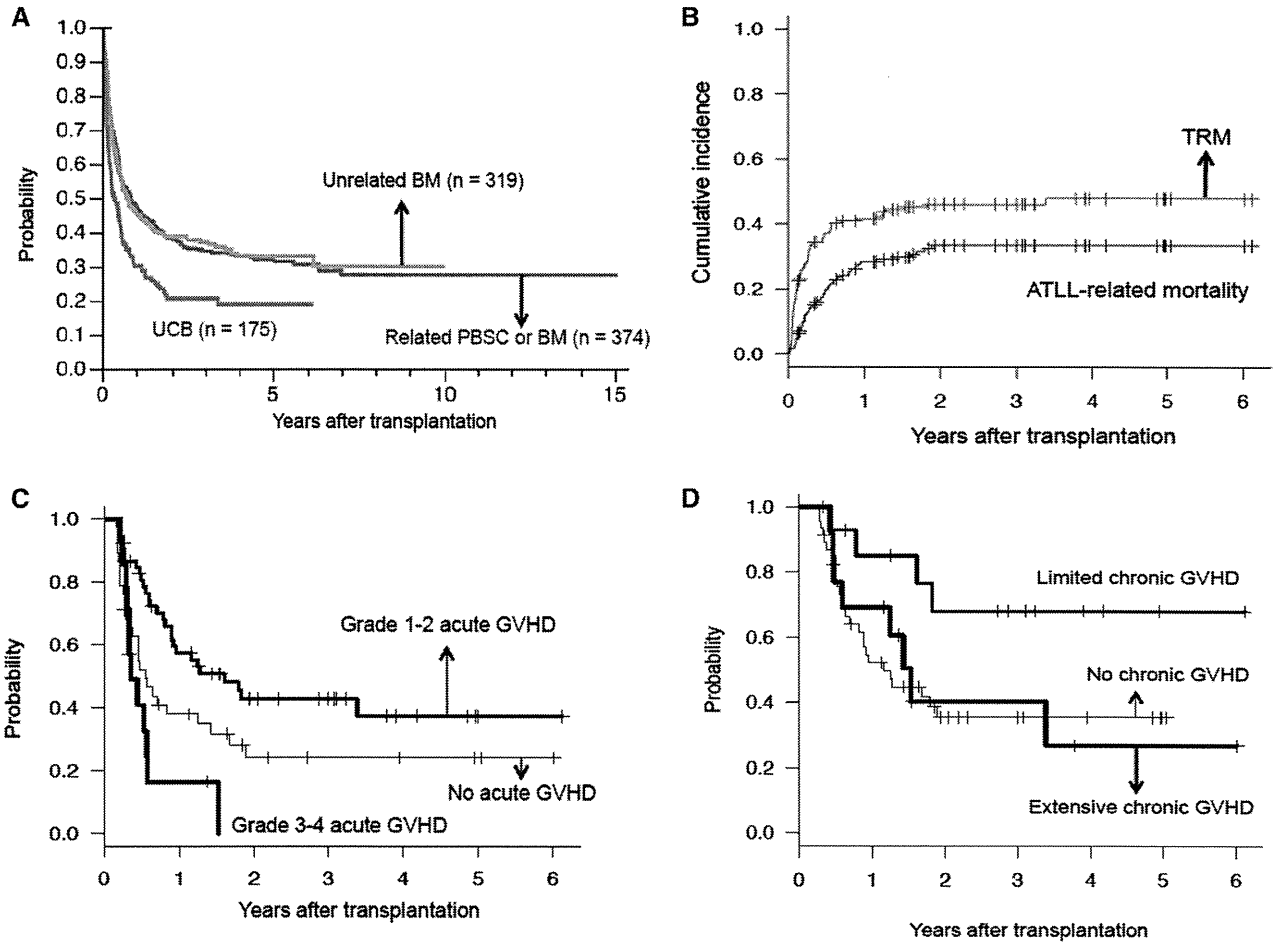

Figure 1. Survival, adult T cell leukemia/lymphoma (ATLL)-related mortality rates, and transplantation-related mortality (TRM) rates of patients receiving cord blood transplantation (CBT). (A) Kaplan-Meier curves of the estimated overall survival rates (OS) of ATLL patients treated with CBT. UCB, umbilical cord blood; PBSC, peripheral blood stem cells; BM, bone marrow, GVHD, graft-versus-host disease. (B) Cumulative incidence curves of ATLL-related mortality and TRM in patients treated with CBT. (C) Landmark plots of OS to determine the effects of acute GVHD. (D) Landmark plots of OS to determine the effects of chronic GVHD.

Table 2
Univariate Analysis of Risk Factors for Overall Survival

Variables		No.	OS		
			Two-Year OS (%)	95% CI	*P* Value
Age 1	<60 yr	134	23.0	15.0-31.0	.080
	≥60 yr	41	12.0	6.0-22.4	
Age 2	<55 yr	85	25.4	15.0-35.8	.100
	≥55 yr	90	15.6	7.0-24.2	
Sex	Female	70	22.3	11.5-33.1	.453
	Male	105	19.4	10.8-28.0	
Disease status at transplantation	CR	50	40.3	25.5-55.1	.003
	Not in CR	116	14.3	7.1-21.7	
Time from diagnosis to transplantation	<200 d	94	22.4	12.8-32.0	.752
	≥200 d	75	19.9	9.7-30.1	
Yr of transplantation	<2005	71	17.6	8.2-27.0	.160
	≥2005	104	23.1	13.5-31.5	
Conditioning regimen	FIC	63	20.2	9.8-30.6	.740
	RIC	108	20.2	11.8-28.6	
Infused nucleated cell dose ($\times 10^7$/kg)	<2	19	10.8	0-29.3	.290
	≥2	145	22.6	14.9-30.3	
Infused CD34 cell dose ($\times 10^5$/kg)	<1	97	23.3	13.9-32.7	.396
	≥1	66	19.1	8.0-30.2	
ABO matching	Matched	56	12.8	3.4-22.2	.024
	Minor mismatched	49	30.5	15.5-45.5	
	Major mismatched	69	20.5	9.9-31.1	
HLA matching	0 mismatched	5	30.0	0-77.4	.525
	1 mismatched	36	21.6	5.6-37.6	
	2 mismatched	73	24.6	14.3-35.9	
	≥3 mismatched	42	18.1	3.9-32.3	
GVHD prophylaxis 1	Cyclosporine-based	90	21.9	12.5-31.4	.710
	Tacrolimus-based	77	20.3	10.0-30.4	
GVHD prophylaxis 2 (cyclosporine/tacrolimus + other drug)	No	70	12.4	4.8-20.0	.003
	Yes	97	32.7	21.1-44.3	
Acute GVHD	No	59	16.8	5.7-27.9	<.0001
	Yes	80	29.4	18.2-40.6	

follows: grade 1, n = 23 patients; grade 2, n = 37 patients; grade 3, n = 14 patients; and grade 4, n = 6 patients. There was no significant difference in OS between patients with grades 1 and 2 GVHD ($P = 1.00$), in contrast to the difference between patients with grades 1 and 3 GVHD ($P = .013$). Moreover, based on the previous national survey analysis of the effect of acute GVHD on survival in patients with ATLL [5,15], the effect of acute GVHD on OS in the present study was evaluated using landmark plots (landmark day 60) according to the following 3 categories: (1) no acute GVHD (n = 38), (2) grade 1 to 2 acute GVHD (n = 53), and (3) grade 3 to 4 acute GVHD (n = 14). The 2-year OS rates for patients according to the acute GVHD grade were as follows: 24.2% (95% CI, 11.2% to 39.8%) without acute GVHD; 42.7% (95% CI, 28.1% to 56.6%) with grade 1 to 2 GVHD; and 0% with grade 3 to 4 GVHD (Figure 1C). These analyses demonstrated that the development of grade 1 to 2 acute GVHD was associated with higher OS compared with the absence of acute GVHD ($P = .048$), whereas the development of grade 3 to 4 acute GVHD was associated with lower OS compared with that in patients with grade 1 to 2 acute GVHD ($P = .0003$). The cumulative 2-year ATLL-related mortality rates according to the GVHD grades were as follows: 32.6% (95% CI, 19.7% to 46.1%) for grade 1 to 2 acute GVHD; 29.8% (95% CI, 8.2% to 55.6%) for grade 3 to 4 acute GVHD; and 45.9% (95% CI, 29.0% to 61.3%) for no acute GVHD. There was a trend toward a lower risk of relapse or progression in those who developed grade 1 to 2 acute GVHD relative to those without GVHD. Among patients with non-CR at transplantation, there was also a trend toward higher 2-year OS (36.7%; 95% CI, 18.7% to 54.9%) in those who developed grade 1 to 2 acute GVHD than in those without GVHD (15.6%; 95% CI, 3.4% to 35.9%). These data suggested a graft-versus-ATLL effect induced by CBT.

Table 3
Multivariate Analysis of Risk Factors for OS

Variables	OS		
	HR	95% CI	*P* Value
Age, yr			
<55	1		
≥55	1.15	.63-2.09	.652
Disease status at transplantation			
CR	1		
Not in CR	1.38	.73-2.63	.190
ABO matching			
Matched	1		
Minor mismatched	.56	.25-1.24	.152
Major mismatched	.77	.39-1.48	.337
GVHD prophylaxis (cyclosporine/ tacrolimus + other drug)			
No	1		
Yes	.76	.42-1.38	.365
Acute GVHD (time-dependent covariate)			
No	1		
Yes	.10	.01-.94	.044

Effects of Chronic GVHD on Survival

Chronic GVHD was evaluated in 74 patients who survived for at least 100 days after transplantation. Chronic GVHD occurred in 28 patients (37%) with a median time to onset of 115 days (range, 73 to 1287 days) after CBT. The effect of chronic GVHD on OS was evaluated using landmark plots (landmark day 100), and the 2-year OS results were as follows: no chronic GVHD (n = 46), 35.6% (95% CI, 21.0% to 50.0%); limited chronic GVHD (n = 15), 68.1% (95% CI, 35.4%

to 86.8%); and extensive chronic GVHD (n = 13), 40.4% (95% CI, 13.4% to 66.4%) (Figure 1D). There was a trend toward a higher OS among patients with limited chronic GVHD, but there were no significant differences relative to patients without chronic GVHD ($P = .10$) and those with extensive chronic GVHD ($P = .12$).

Cause of Death

At the last follow-up, 46 patients remained alive and 129 were deceased. The median follow-up time among the survivors was 22.5 months (range, 0 to 74.5 months). Disease progression (n = 52) was the leading cause of death. Infection was the cause of death in 40 patients (31%; bacterial, n = 27 patients; fungal, n = 3; viral, n = 8; and others, n = 2). Viral infection-related deaths were caused by the following pathogens: cytomegalovirus, n = 3; adenovirus, n = 2; human herpesvirus-6, n = 2; and varicella-zoster virus, n = 1. Among the 27 patients who succumbed to bacterial infection, 16 died before engraftment at a median of 17 days after CBT (range, 7 to 38 days). Among the 20 patients who developed severe acute grade 3 to 4 GVHD, 2 remain alive without disease progression. However, 9 of the 20 patients died of GVHD, 5 of disease progression, and 4 of infection.

The Fine and Gray proportional hazards model was applied to identify the variables affecting ATLL-related mortality and TRM. The pretransplantation variables included age, gender, disease status at CBT, days from diagnosis to transplantation, age at transplantation, conditioning regimen, number of infused nucleated cells, ABO compatibility, HLA compatibility, and GVHD prophylaxis. The following pretransplantation factors associated with a higher risk of ATLL-related mortality were identified in a multivariate analysis: not in CR at CBT (HR, 3.37; 95% CI, 1.12 to 10.2; $P = .032$) and an age > 55 years at CBT (HR, 2.32; 95% CI, .98 to 5.48; $P = .054$). The following pretransplantation factors were associated with a marginally higher risk of TRM: lower number of infused nucleated cells ($\geq 2 \times 10^7$/kg versus $< 2 \times 10^7$/kg; HR, .56; 95% CI, .30 to 1.02; $P = .059$) and GVHD prophylaxis with a calcineurin inhibitor alone (additional agents plus calcineurin inhibitors versus calcineurin inhibitors alone; HR, .60; 95% CI, .34 to 1.07; $P = .064$).

DISCUSSION

We present here the results of the largest retrospective study of ATLL patients receiving CBT; these results have extended our knowledge relative to that gained from other studies, which were limited by the numbers of cases [15,20,21]. Because graft source selection is strongly influenced by the donor availability, it is difficult to directly compare the outcomes of CBT with those of other allo-HSCT modalities. Nevertheless, the outcome of CBT for ATLL in the previous nationwide survey, with a 3-year OS rate of 17%, was clearly unsatisfactory because the study period corresponded with the developmental phase of CBT in adult patients [15]. Recent improvements in the outcome of CBT have been expected after optimization of the number of cells used for CBT and the improved HLA-compatibility of cord blood units [29-31]. Consequently, a recent nationwide survey data of adults with acute non-ATLL leukemia revealed no differences in the outcome of CBT in comparison with those of other allo-HSCT modalities [18,19]. However, the updated data (through December 2009) indicated that CBT for ATLL remained associated with a poorer 3-year OS of 20.6%, compared with OS of 34.4% among the 374 patients who received related BM or PBSC and 37.1% among the 319 patients who received unrelated BM ($P < .0001$) (Figure 1A). Therefore, the aim of the present study focused on the feasibility of CBT in the context of a larger cohort of patients with ATLL.

In the present study, 2 important findings were identified regarding CBT for ATLL. First, CBT cured patients with ATLL partly through a graft-versus-ATLL effect. Second, the high rate of TRM (approximately 50%) remains a significant problem. The OS curve for ATLL patients who received CBT reached a plateau by 3 years, suggesting long-term survival of selected patients, although the outcome of CBT for ATLL (3-year OS, 20%) did not compare favorably with those of other allo-HSCT modalities. Regarding the prognostic factors affecting survival, our present univariate analysis identified the 5 following significant variables associated with higher OS: (1) age, (2) disease status at transplantation, (3) ABO compatibility, (4) addition of agents such as MTX or MMF to calcineurin inhibitors for GVHD prophylaxis, and (5) development of acute GVHD. Further, the multivariate analysis revealed that the development of acute GVHD was independently associated with better OS relative to the absence of acute GVHD. A landmark analysis showed that the development of grade 1 to 2, or so called mild-to-moderate acute GVHD, was associated with better OS when compared with the absence of acute GVHD. There was also a trend toward a lower risk of relapse or progression with the development of acute GVHD when compared with the absence of GVHD and better OS in patients with limited chronic GVHD. Taken together, these data suggest the presence of a curative graft-versus-ATLL effect conferred by CBT.

However, it is typically difficult for physicians to optimize the effects of acute GVHD to prevent disease progression via graft-versus-ATLL. Therefore, a more realistic attempt would be the control of pretransplantation factors that might affect the CBT outcome and, thus, enhance the benefit of allo-HSCT. The multivariate analysis performed herein with respect to ATLL-related deaths identified disease status at CBT as the most important factor. ATLL usually resists conventional chemotherapy and must be treated soon after diagnosis because of the rapid proliferation of tumor cells, which generates a high tumor burden [2,3]. In the future, novel agents, such as mogamulizumab, a humanized anti-CCR4 monoclonal antibody, might improve CBT-associated survival by decreasing the tumor burden before transplantation [32-35]. Another possibility for improving survival might be reducing the time from diagnosis to transplantation while patients with ATLL remain chemosensitive. Moreover, CBT provides a considerable advantage for patients who require urgent allo-HSCT to combat aggressive ATLL.

In the present study, we have shown that CBT is feasible and curative. However, the high rate of TRM remained a significant problem. Bacterial infection caused the highest incidence of death (21%) during the neutropenic period. The infusion of lower numbers of nucleated cells ($< 2 \times 10^7$/kg), which is usually associated with delayed engraftment, was marginally associated with TRM. Neutrophil recovery is slower in patients treated via CBT, and immunosuppressed patients with ATLL might be at an increased risk of developing more frequent opportunistic infections [36]. Improved supportive care to prevent bacterial infection is required after CBT for patients experiencing a prolonged neutropenic period. The ongoing development of better graft engineering [37] or double-CBT [38] might facilitate rapid neutrophil recovery and, thus, help to reduce the TRM rate in CB recipients.

The present study has several limitations. First, our results concerning the effect of chronic GVHD on survival should be interpreted with caution because the relatively small number of patients who developed chronic GVHD did not allow us to evaluate the effect of this condition on survival in a multivariate analysis. Instead, we were limited to performing a landmark analysis of OS according to the severity of chronic GVHD. Certainly, we detected a trend toward higher OS in patients with limited chronic GVHD when compared with patients without chronic GVHD, suggesting the possible presence of a graft-versus-ATLL effect. However, these results might be biased because of insufficient statistical power. Our future studies will assess the effect of chronic GVHD on the outcome of CBT for the treatment of ATLL after a long-term follow-up. Although the present study employed, to our knowledge, the largest cohort of CBT-treated patients to date and our results demonstrated that CBT is a feasible and effective treatment, this was a retrospective analysis. Therefore, this finding requires confirmation in prospective studies. To establish reliable criteria for CBT administration, a prospective multicenter clinical trial is underway in Japan to evaluate the safety and efficacy of CBT combined with Flu, Mel, and low-dose TBI (4 Gy) along with GVHD prophylaxis (tacrolimus and MMF [39]).

In conclusion, CBT is feasible and effective for patients with ATLL and acts via a graft-versus-ATLL effect. However, the outcome of CBT is unsatisfactory when compared with those of other allo-HSCT modalities. The high rate of TRM must be reduced, and the development of novel strategies is required to further improve the outcome of CBT.

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A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L

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Background: Thymic carcinoma (TC) is an exceptionally rare tumor, which has a very poor prognosis differing from thymoma. Till date, there has been no report of any results of clinical trials focusing on TC. The role of non-anthracycline-based chemotherapy has not been elucidated since the previous studies included a relatively small number of TC patients. This single-arm study evaluated carboplatin and paclitaxel (CbP) in chemotherapy-naive patients with advanced TC.

Patients and methods: The study treatment consisted of carboplatin (area under the curve 6) and paclitaxel (200 mg/m^2) every 3 weeks for a maximum of six cycles. The primary end point was objective response rate (ORR) by independent review. The secondary end points included overall survival (OS), progression-free survival (PFS), and safety. Based on the SWOG 2-stage design, the planned sample size of 40 patients was determined to reject the ORR of 20% under the expectation of 40% with a power of 0.85 and a type I error of 0.05.

Results: Forty patients from 21 centers were enrolled for this study from May 2008 to November 2010. Of the 39 patients evaluable for analysis, 36 were pathologically diagnosed by independent review, and 97% patients were eventually TC. There was 1/13 complete/partial responses with an ORR of 36% (95% confidence interval 21%–53%; $P = 0.031$). The median PFS was 7.5 (6.2–12.3) months, while OS did not reach the median value. Major adverse event was grade 3–4 neutropenia in 34 patients (87%). There was no treatment-related death.

Conclusions: In this largest trial with TC, CbP showed promising efficacy in advanced TC when compared with anthracycline-based chemotherapy, which is the current standard treatment of thymic neoplasm. Our results established that CbP, one of the standard treatments for non-small-cell lung cancer, might be an option as a chemotherapy regimen for TC.

Key words: advanced thymic carcinoma, the standard treatments for non-small-cell lung cancer, carboplatin, paclitaxel

introduction

Thymoma is a rare tumor originating from the epithelial cells of the thymus, and is best known for its association with the neuromuscular disorder myasthenia gravis. According to data from the US National Cancer Institute Surveillance, Epidemiology and End Results Program, thymoma has an annual incidence of 0.15 cases in the USA [1] and 0.32 cases in the Netherlands [2] per 100 000 person-years. Thymic carcinoma (TC) is a very rare type of thymic epithelial neoplasm, but there are no reliable data on its incidence. A frequent subtype of TC is squamous cell carcinoma [3, 4]. Typically, TC is invasive and aggressive with a high risk of death, whereas other thymic neoplasms are indolent tumors with a tendency toward local recurrence rather than metastasis. A retrospective survey of 1320 patients reported that TC had a significantly worse prognosis than thymoma and thymic carcinoid [4]. TC has been classified as a distinct entity from thymoma in the World Health Organization (WHO) classification 2004 [5]. However, a severe rarity of TC led previous studies to lump both TC and thymoma together; the clinical evaluations of ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide), CAP

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