Disclosure

The authors have stated that they have no conflicts of interest.

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PHASE II STUDIES

Pemetrexed and carboplatin followed by pemetrexed maintenance therapy in chemo-naïve patients with advanced nonsquamous non-small-cell lung cancer

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Summary *Introduction* This study prospectively evaluated the efficacy and safety of pemetrexed and carboplatin followed by maintenance pemetrexed in chemo-naïve patients with advanced nonsquamous non-small cell lung cancer (NSCLC). *Methods* A total of 109 patients received pemetrexed (500 mg/m^2) and carboplatin (area under the curve = 6 mg/mL·min) every 21 days. For patients without disease progression after 4 cycles, pemetrexed was continued until disease progression or unacceptable toxicity. Pre-planned subgroup analysis results based on the presence of epidermal growth factor receptor (*EGFR*) mutations are also presented. *Results* The median number of treatment cycles was 5 (range: 1–30) in the entire study period. Most of the grade ≥3 toxicities observed were hematologic in nature, with no increase in

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the relative incidence associated with continuation maintenance therapy with pemetrexed. Among the 106 total patients assessable for efficacy, the objective response rate was 35.8 %, median progression free survival (PFS) 5.7 months, and median overall survival (OS) 20.2 months. Sixty patients received maintenance pemetrexed (median: 4 cycles, range: 1–26 cycles); median PFS from the beginning of induction treatment was 7.5 months. From the subgroup analysis for *EGFR* mutation status, the median OS of *EGFR* wild-type patients (n=61) was 20.2 months. *Conclusions* Pemetrexed/carboplatin followed by pemetrexed was well tolerated and active for front-line treatment of advanced nonsquamous NSCLC. Encouraging survival outcomes were observed even in *EGFR*-wild type patients.

Keywords Pemetrexed · Carboplatin · Continuation maintenance · Nonsquamous NSCLC · *EGFR* mutation status

Introduction

Lung cancer is the most common type of cancer globally and the leading cause of cancer death [1]. Approximately 85 % of patients with lung cancer have non-small cell lung cancer (NSCLC), and 70 % of NSCLC is inoperable, locally advanced, or metastatic [2]. Currently, nonsquamous histology has been an important determinant for clinical outcome in NSCLC patients treated with pemetrexed or bevacizumab chemotherapy [3–8]. In addition, oncogenic driver mutations, such as *EGFR* mutation and fusions of echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK), were found in a subset of patients with nonsquamous NSCLC. A higher proportion of tumors harboring *EGFR* mutations were reported in East Asian compared with Caucasian patients [9]. While some molecular-targeted agents, such as gefitinib, erlotinib and crizotinib, have dramatically improved overall survival in the population harboring these targetable oncogenic gene alterations, prognosis of the other wild-type patients with NSCLC remains to be improved [10–16].

Pemetrexed, a potent multitargeted antifolate, inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, all of which are involved in the *de novo* synthesis of purines or pyrimidines [17]. Pemetrexed is the key drug in the treatment for nonsquamous NSCLC patients, showing consistently superior efficacy compared with standard treatments [4–7]. Recently, a new treatment paradigm using pemetrexed for continuation maintenance therapy after 4 cycles of pemetrexed/cisplatin has been reported in a large phase III trial [18]. Continuation maintenance therapy with pemetrexed improved PFS and OS in patients with advanced nonsquamous NSCLC compared with placebo.

While pemetrexed/cisplatin followed by pemetrexed maintenance therapy is the standard treatment in nonsquamous NSCLC, carboplatin-based regimens have been widely used as a substitute for cisplatin-based regimens due to their lower toxicity and more convenience for administering in outpatient treatment settings. However, clinical outcomes of continuation therapy with pemetrexed following pemetrexed in combination with carboplatin have not fully been addressed. This study was conducted to evaluate efficacy, including the survival outcome and safety of pemetrexed/carboplatin combination therapy followed by continuation maintenance with pemetrexed in chemo-naïve patients with advanced nonsquamous NSCLC. Given that *EGFR* mutation status has recently become a key factor for the overall treatment plan of advanced NSCLC, we also assessed the efficacy data according to the *EGFR* mutation status using a pre-planned analysis.

Materials and methods

Eligibility

Patients 20 years of age or older with histologically or cytologically confirmed advanced NSCLC, other than predominantly squamous cell histology, were eligible for the study. Each patient was required to have clinical stage IIIB, stage IV or recurrent disease, a lesion not amenable to curative radiation, and no history of prior chemotherapy [19]. Eligibility stipulated an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate function of the lungs, bone marrow, liver, and kidneys. The criteria for organ function specified baseline resting arterial oxygen saturation (SpO_2) on room air ≥93 %; hemoglobin ≥9.0 g/dL, white blood cells ≥3000/mm^3, neutrophils ≥1500/mm^3, platelets ≥100,000/mm^3, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, creatinine ≤1.5 times ULN, and 24-h creatinine clearance or calculated creatinine clearance ≥45 mL/min as estimated by the Cockcroft and Gault formula. Patients were required to have a life expectancy of at least 12 weeks and no brain metastases other than stable, asymptomatic, or treated metastatic brain tumors. This study was conducted following good clinical practices and the ethical principles outlined in the Declaration of Helsinki. This study protocol was approved by the institutional review board at each participating center. All patients signed written informed consent before enrollment. The trial has been registered under the number NCT 01020786.

Study design and treatment

This was an open-label, multicenter, single arm, prospective postmarketing study. The primary objective was to evaluate

the efficacy, as measured by PFS, of this study treatment in patients with advanced nonsquamous NSCLC who received at least one dose of the initial combination therapy. Secondary endpoints, including OS, disease control rate (DCR), overall response rate (ORR), and safety, were also evaluated.

Eligible patients received pemetrexed 500 mg/m^2 through a 10-min intravenous infusion followed by intravenous infusion of carboplatin at a dose corresponding to target area under the curve (AUC) equal to 6 mg/mL·min (AUC6) over at least 30 min on day 1. This combination therapy was repeated every 21 days for up to 4 cycles. After 4 cycles, patients with complete response (CR), partial response (PR), or stable disease (SD) received maintenance therapy with pemetrexed 500 mg/m^2 every 21 days until evidence of disease progression or development of unacceptable toxicities. All patients received oral folic acid (0.5 mg) daily and a vitamin B_{12} (1 mg) injection every 9 weeks, beginning at least 1 week before the first dose and continuing until 3 weeks after the last dose of study treatment.

Subsequent cycles of treatment were withheld until the following criteria were satisfied: neutrophil count ≥1500/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥8.0 g/dL, ECOG performance status ≤1, SpO_2 ≥93 %, AST/ALT ≤2.5 times ULN, total bilirubin ≤1.5 times ULN, and 24-h creatinine clearance or calculated creatinine clearance ≥45 mL/min as estimated by the Cockcroft and Gault formula, other tolerable nonhematologic toxicity, and a decision by the physician. If these criteria were not satisfied within 29 days from the date of dose administration in the cycle because of adverse events, the pemetrexed dose was reduced from 500 to 400 mg/m^2 or from 400 to 300 mg/m^2, and the carboplatin dose was reduced from AUC6 to an AUC of 5 mg/mL·min (AUC5) or from AUC5 to an AUC of 4 mg/mL·min (AUC4). Any patient who required a third dose reduction was withdrawn from the study. In addition, if the next cycle had not started within 43 days from previous dosing due to toxicity, the patient was discontinued.

Baseline and treatment assessments

Baseline evaluations included medical history, physical examination, electrocardiogram, tumor status, ECOG performance status, clinical laboratory test, and *EGFR* mutation status. Testing for *EGFR* mutations was outsourced from each institution to commercial clinical laboratories in Japan. Computed tomography was performed for tumor assessment within 21 days of initiation of study treatment and was repeated every 6 weeks thereafter. All responses were defined according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.0. If a patient was documented as having a CR or a PR, a confirmatory evaluation was performed after an interval of at least 4 weeks. The patient was considered to have SD if it was confirmed and sustained for 6 weeks or longer after the start of study treatment. PFS was defined as the time from enrollment to the date of confirmation of progressive disease (PD) or the date of death from any cause (whichever occurs earlier). Patients who received any subsequent systemic anticancer therapy prior to objective PD or death would be censored at the date of the last objective progression-free disease assessment prior to starting the subsequent systemic anticancer therapy. Overall survival was defined as the time from enrollment until death from any cause. For patients with unknown death status, OS would be censored at the last date the patient was known to still be alive.

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical methods

The sample size of 100 patients had a power of 90 % at a one-sided type I error rate of 0.05 to compare PFS of this study regimen versus the first-line platinum-based combination therapy as a constant value under the following assumptions: the expected PFS of the first-line therapy of platinum-based combination regimen was 5 months, the expected PFS of this study treatment was 7 months, the enrollment period was 8 months, and the follow-up period was 12 months.

Efficacy and safety analyses were planned to be performed on patients who received at least one dose of the treatment. Since some patients had significant protocol violations during the study, they were excluded from the efficacy analysis prior to the database lock. In this manuscript, the efficacy was assessed on the latter data set.

Time-to-event variables were analyzed using Kaplan-Meier estimation techniques, including Kaplan-Meier curves, quartiles, and interval estimation using 90 % and 95 % confidence intervals (CIs). For DCR and ORR, 95 % CIs were calculated using the exact test. Prespecified subgroup analyses for PFS and ORR based on *EGFR* mutation status were also included.

Results

Patient characteristics

Patient disposition is shown in Fig. 1. Between December 2009 and July 2010, 111 patients with recurrent or newly diagnosed, advanced nonsquamous NSCLC were enrolled at 25 clinical sites in Japan. Two patients were subsequently discontinued from the study for not meeting entry criteria, and 109 patients received the study treatment. Baseline characteristics are summarized in Table 1. The median age for the treated population was 63 years (range: 38–78 years), and 40 patients (36.7 %) were female. Other key characteristics at baseline included

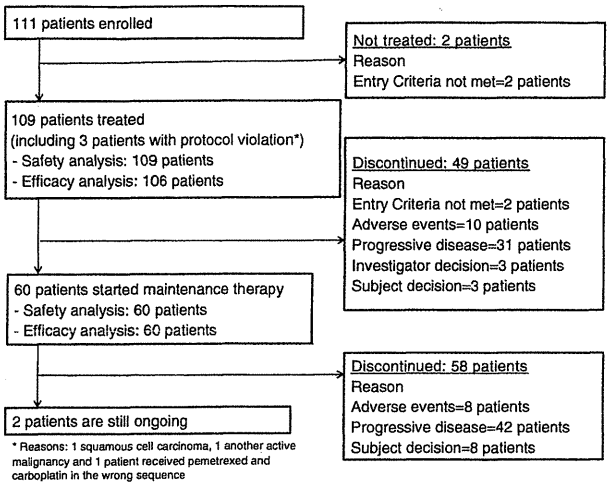

Fig. 1 Patient disposition

adenocarcinoma histology (97.2 %) and stage IV disease (66.1 %).

Treatment delivery

Patients received a median of 5 cycles (range: 1–30) of treatment in the entire study period, with 75 patients (68.8 %) completing at least 4 cycles. After completion of 4 cycles of carboplatin and pemetrexed combination therapy, 60 patients (55.0 %) continued pemetrexed monotherapy with a median of 4 cycles (range: 1–26) in the maintenance period. The remaining 15 patients did not receive pemetrexed maintenance therapy due to disease progression (8 cases), adverse events (4 cases), investigator decision (2 cases), or patient decision (1 case).

Overall, 30 patients (27.5 %) out of 109 experienced dose reductions, and 66 patients (60.6 %) experienced dose delay due to adverse events, mainly due to myelosuppression. Among the 60 patients in the maintenance period, 10 patients (16.7 %) had a dose reduction, and 33 patients (55.0 %) had a dose delay due to toxicities.

Table 1 Patient characteristics

Characteristics	*N*=109	%
Age (yr)		
Median	63	–
Range (min, max)	38–78	–
Gender (*n*)		
Male	69	63.3
Female	40	36.7
Performance status (*n*)		
0	37	33.9
1	72	66.1
Disease stage (*n*)		
IIIB	33	30.3
IV	72	66.1
Recurrence	4	3.7
Histology (*n*)		
Adenocarcinoma[a]	106	97.2
Large cell lung carcinoma	3	2.8
EGFR mutation status (*n*)		
Positive	24	22.0
Negative	63	57.8
Unknown	3	2.8
Not done	19	17.4

[a] One patient's tumor was reclassified as squamous cell carcinoma after study entry, and the examination of *EGFR* gene type was not done

Efficacy

Out of 109 patients, 106 were evaluable for efficacy analysis. Three patients were excluded for the following reasons: revised diagnosis of squamous cell carcinoma during the study (1 patient), diagnosis of another active malignancy (1 patient), and delivery of pemetrexed and carboplatin in the wrong sequence during the initial combination period (1 patient). There were 38 partial responses and no complete responses, yielding an ORR of 35.8 % (95 % CI: 26.8 %–45.7 %) (Table 2). Forty-one patients (38.7 %) had stable disease, yielding an overall DCR (CR + PR + SD) of 74.5 % (95 % CI: 65.1 %–82.5 %) (Table 2). At the median follow-up period of 18.5 months (range: 2.1–24.4 months), the median PFS and OS were 5.7 months (95 % CI: 4.4–7.3 months) and 20.2 months (95 % CI: 16.7 months–not calculable), respectively (Table 2 and Fig. 2).

Among 60 patients who received continuation maintenance with pemetrexed, the median PFS from the beginning of induction treatment was 7.5 months (95 % CI: 6.5–8.3 months); median OS was not calculable, with a 1-year survival rate of 89.7 %. In the 46 patients who discontinued study treatment before receiving pemetrexed maintenance, on the other hand, the median PFS was 2.8 months (95 % CI: 2.2–3.0 months), median OS was 8.6 months (95 % CI: 5.7–14.3 months) and 1-year survival rate was 46.8 %.

Sub-group analysis: *EGFR* mutation status

In the present study, *EGFR* mutation status was evaluated in 85 (80 %) of 106 patients evaluable for efficacy; 24 patients harbored an activating *EGFR* gene mutation, whereas 61 patients were *EGFR* wild-type. We prospectively performed subgroup analysis of efficacy according to *EGFR* mutation status. The ORR in the patients with and without *EGFR* mutations were 37.5 % (95 % CI: 18.8 %–59.4 %) and 36.1 % (95 % CI: 24.2 %–49.4 %), respectively (Table 2). The median PFS was 5.7 months (95 % CI: 5.2–7.2 months)

Table 2 Treatment outcome

		EGFR mutation	
Entire period	Total (N=106)	Positive (N=24)	Negative (N=61)
Median PFS, mo	5.7	5.7	6.9
95 % CI	4.4–7.3	5.2–7.2	4.3–7.8
Median OS, mo	20.2	Not calculable	20.2
95 % CI	16.7–Not calculable	20.2–Not calculable	14.2–Not calculable
Overall best response, *n* (%)			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	38 (35.8)	9 (37.5)	22 (36.1)
Stable disease	41 (38.7)	8 (33.3)	27 (44.3)
Progressive disease	20 (18.9)	3 (12.5)	10 (16.4)
Not evaluable	7 (6.6)	4 (16.7)	2 (3.3)
Overall response rate, *n* (%)	38 (35.8)	9 (37.5)	22 (36.1)
95 % CI	26.8–45.7	18.8–59.4	24.2–49.4
Disease control rate, *n* (%)	79 (74.5)	17 (70.8)	49 (80.3)
95 % CI	65.1–82.5	48.9–87.4	68.2–89.4

CI confidence interval, *PFS* progression-free survival, *mo* month(s), *OS* overall survival

for *EGFR* mutation-positive patients and 6.9 months (95 % CI: 4.3–7.8 months) for *EGFR* wild-type patients (Table 2). At the time of analysis, the median OS was not calculable for *EGFR* mutation-positive patients, but 1-year survival rate was 95.7 %; the median OS of patients with *EGFR* wild-type tumors was 20.2 months (95 %CI: 14.2 months-not calculable) with a 1-year survival rate of 68.1 % (Table 2 and Fig. 3a). In *EGFR* wild-type patients, the median OS of those who were treated with pemetrexed continuation maintenance (n=37) was notably longer compared with that of 24 patients who did not continue pemetrexed maintenance, whereas OS results in the patients who harbored *EGFR* activating mutation were similar among those with (n=14) or without (n=10) maintenance therapy using pemetrexed (Fig. 3b).

Safety

All 109 patients who received the initial combination therapy were assessable for safety analysis. The major adverse events for each treatment period (entire, initial combination, and maintenance periods) are shown in Table 3. Hematologic toxicities reaching ≥ grade 3 were neutropenia (56.0 %), thrombocytopenia (41.3 %), anemia (29.4 %), and leukopenia (22.0 %). Nonhematologic toxicities observed in more than half of patients included appetite loss (75.2 %), nausea (74.3 %), fatigue (67.9 %), and ALT increased (51.4 %), but the incidence of toxicities of grade 3 or higher was less than 10 %. The majority of adverse events were observed during the initial 4 cycles of pemetrexed and carboplatin combination therapy. Common toxicities ≥ grade 3 observed in the maintenance period were similar to those observed during the initial combination treatment period, including neutropenia (38.3 %), thrombocytopenia (16.7 %), leukopenia (11.7 %), and anemia (10.0 %). Newly emerged or deteriorated toxicities during maintenance periods were rarely observed. No treatment-related deaths were reported in this study.

Discussion

This was a prospective, multicenter clinical study of first-line combination therapy with pemetrexed and carboplatin followed by maintenance therapy with pemetrexed in chemo-naive patients with advanced nonsquamous NSCLC. This regimen achieved a response rate of 35.8 %, median PFS of 5.7 months, and median OS of 20.2 months. Although the lower limit of one-sided 95 % CI of PFS seen in this trial (4.4 months) did not exceed the prior assumption of a median PFS of 5.0 months, the survival results were striking. Since patients with *EGFR*-mutation positive advanced NSCLC had dramatically improved survival outcomes following treatment with *EGFR* tyrosine kinase inhibitors, the proportion of such patients in this trial may have had an impact on this favorable survival outcome [10–14]. However, the median OS of 20.2 months in 61 *EGFR* wild-type patients was much longer than expected [13], which was still encouraging.

Our study also confirmed findings from an earlier phase II study which showed excellent tolerability of the pemetrexed/carboplatin combination as a first-line chemotherapy [20]. Similarly, our study supported both the safety of

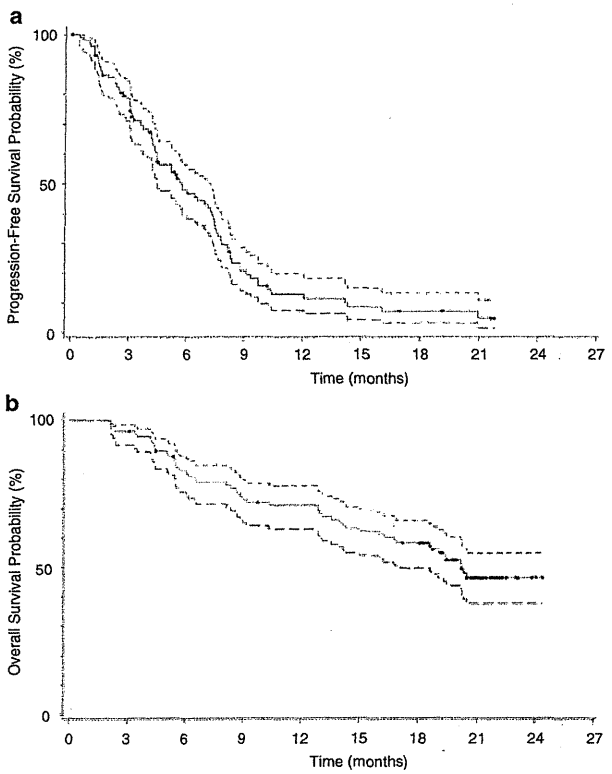

Fig. 2 **a.** Kaplan-Meier curves for progression-free survival curve (*solid line*) with 95 % confidence band (*dashed lines*). **b.** Kaplan-Meier curves for overall survival curve (*solid line*) with 95 % confidence band (*dashed lines*)

pemetrexed and carboplatin as an initial therapy for advanced nonsquamous non-small-cell lung cancer, and also the feasibility of pemetrexed as a maintenance therapy in these patients. The most common hematologic toxicity reaching grades 3 or 4 was neutropenia, but febrile neutropenia occurred in only 1 case. Grade 3 or 4 thrombocytopenia was also frequently observed and 7.3 % of patients received platelet transfusion. However, this condition was considered manageable without any severe bleeding events. There was also no increase in the incidence of hematologic toxicities associated with continuation maintenance with pemetrexed. With regard to nonhematologic toxicity, there were no grade 3 or 4 toxicities encountered in >10 % of patients throughout the study treatment. No unexpected toxicities were observed.

Pemetrexed is used in the maintenance setting for advanced nonsquamous NSCLC, following the results of the PARAMOUNT study, in which continuation maintenance therapy with pemetrexed following induction therapy with pemetrexed/cisplatin resulted in significantly improved PFS and OS [18, 21]. In the present study, the favorable tolerability profile of pemetrexed maintenance after induction of pemetrexed/carboplatin is reflected in the observation that 55 % of patients were able to continue on pemetrexed monotherapy with a median of 4 cycles. The median PFS of 7.5 months from the beginning of induction treatment in 60 patients who received maintenance therapy with pemetrexed is consistent with the finding of the PARAMOUNT study where a median PFS of 6.9 months was achieved by continuation maintenance with pemetrexed [18]. Although there are limitations when comparing results from different studies, these data suggest that pemetrexed continuation maintenance therapy is effective whether cisplatin or carboplatin is used for the induction chemotherapy. In our ad-hoc exploratory analyses, *EGFR* wild-type patients who continued with pemetrexed as a maintenance therapy demonstrated marked OS compared with those who did not receive maintenance therapy, whereas there was no obvious difference in OS of 24 *EGFR*-mutation positive patients, regardless of maintenance treatment. Given that most these patients (10 of 14 patients with pemetrexed maintenance, 9 of 10 patients without maintenance) received gefitinib or erlotinib as poststudy treatment, a good outcome could have been achieved in patients harboring the targetable oncogenic gene alterations by subsequent treatment with these active therapies, even though they did not continue pemetrexed maintenance. Although this study was not a

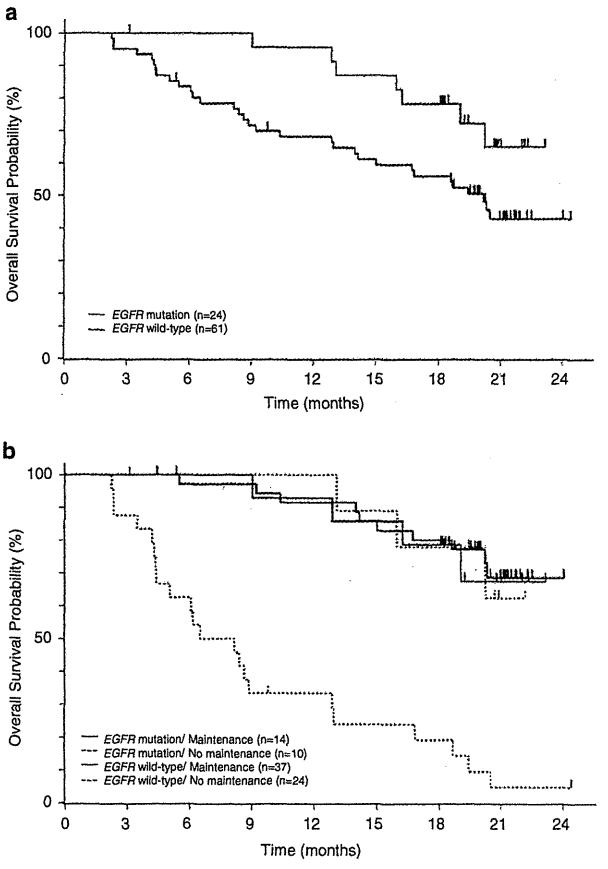

Fig. 3 **a.** Overall survival by EGFR mutation status. **b.** Overall survival by EGFR mutation status and maintenance-treated status

Table 3 Toxicity by treatment period

	Entire period (*N*=109)			Initial combination period (*N*=109)			Maintenance period (*N*=60)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic	*n*(%)	*n*(%)	*n* (%)	*n*(%)	*n* (%)	*n* (%)	*n* (%)	*n*(%)	*n* (%)
Leukopenia	83 (76.1)	24 (22.0)	–	82 (75.2)	23 (21.1)	–	43 (71.7)	7 (11.7)	–
Neutropenia	86 (78.9)	47 (43.1)	15 (13.8)	84 (77.1)	45 (41.3)	14 (12.8)	44 (73.3)	21 (35.0)	3 (5.0)
Thrombocytopenia	94 (86.2)	30 (27.5)	15 (13.8)	94 (86.2)	30 (27.5)	15 (13.8)	40 (66.7)	10 (16.7)	–
Anemia	98 (89.9)	32 (29.4)	2 (1.8)	98 (89.9)	31 (28.4)	2 (1.8)	52 (86.7)	8 (13.3)	–
	Any Grade	Grade ≥3		Any Grade	Grade ≥3		Any Grade	Grade ≥ 3	
Non-hematologic	*n* (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
Appetite loss	82 (75.2)	6 (5.5)		81 (74.3)	6 (5.5)		21 (35.0)	–	
Nausea	81 (74.3)	1 (0.9)		80 (73.4)	1 (0.9)		21 (35.0)	–	
Vomiting	42 (38.5)	3 (2.8)		42 (38.5)	3 (2.8)		4 (6.7)	–	
Fatigue	74 (67.9)	2 (1.8)		69 (63.3)	2 (1.8)		33 (55.0)	–	
Rash	32 (29.4)	1 (0.9)		29 (26.6)	1 (0.9)		6 (10.0)	–	
Fever	22 (20.2)	1 (0.9)		20 (18.3)	1 (0.9)		3 (5.0)	–	
Alopecia	8 (7.3)	–		8 (7.3)	–		3 (5.0)	–	
Neuropathy	10 (9.2)	–		7 (6.4)	–		5 (8.3)	–	
ALT increased	56 (51.4)	7 (6.4)		49 (45.0)	5 (4.6)		30 (50.0)	3 (5.0)	
AST increased	55 (50.5)	2 (1.8)		43 (39.4)	1 (0.9)		34 (56.7)	1 (1.7)	

ALT alanine aminotransferase, *AST* aspartate aminotransferase

randomized trial, these results may stimulate further interest in the clinically relevant efficacy of pemetrexed maintenance in *EGFR* wild-type patients for whom the limited therapeutic options exist.

In conclusion, this study regimen of pemetrexed/carboplatin followed by pemetrexed maintenance is feasible and effective as a first-line treatment for advanced nonsquamous NSCLC patients. Our findings have strengthened the rationale for the ongoing randomized phase III trial comparing this regimen with the carboplatin, paclitaxel and bevacizumab combination in patients with advanced, nonsquamous NSCLC [22].

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小児白血病

Pediatric leukemia

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Key words：急性リンパ性白血病，小児，層別化治療

はじめに

小児白血病の70％を占める急性リンパ性白血病(ALL)は，化学療法で治癒に導くことができた最初の悪性腫瘍であり，臨床試験の積み重ねによって治療成績の向上が図られて常にがん化学療法による治療構築の先駆けとなってきた．また，生存率が10％に達しない1960年代初頭からtotal therapyの概念が導入され，以来，一貫して治癒を目指した多剤併用療法の臨床試験が行われている．現在では，初回治療の無イベント生存率(EFS)が80％を超え，5年全生存率は90％に達している[1,2]．この治療成績の向上は，主に1980年以前に開発された抗がん薬の使い方の工夫によって得られたものであり，予後因子の解明や診断技術の向上によって高い精度の治療層別法が開発され，支持療法の進歩によって安全に治療の強化が可能になり，難治例には，造血幹細胞移植(SCT)によってある程度の救済が期待できるようになった．更に近年，分子標的薬など有望な新規治療薬が開発され，ゲノム解析の進歩で難治例の遺伝子異常の背景が詳らかにされつつあり[3]，一層の治癒率向上が期待される．一方，治癒率の向上の結果，小児がん経験者の長期的影響の実態が明らかになり，問題となっている．治癒を期待できる患者においては晩期合併症のない自立した社会人として世に送り出すことが治療のゴールになってきており，トータルケアの重要性が認識されている．なお，小児の急性骨髄性白血病(AML)や慢性骨髄性白血病(CML)は，ダウン症に伴うAMLを除いて成人白血病に薬物療法が類似していることから，本稿では小児ALLの薬物療法に絞ってその動向と展望を述べる．

1 小児ALLの治療選択アルゴリズム

小児ALLの治療は，これまでに明らかにされた予後因子を組み合わせてリスク分類に沿って層別化された治療が行われる(**図1**)[4]．成熟B細胞性ALL(Burkitt白血病)は，小児ALLの1－2％を占め，細胞回転が速く，耐性獲得が速いため，独自に短期決戦型化学療法が開発されて好成績が得られている．次に，有効な分子標的薬が登場したフィラデルフィア染色体(Ph)陽性ALLが層別される．イマチニブを化学療法と併用して長期に投与することで80％を超える3年EFSが得られており，同種SCTなしで治癒が期待できる可能性が示唆されている．次に，予後不良因子である*MLL*遺伝子再構成に特徴づけられる乳児ALLが層別される．*MLL*遺伝子再構成を伴わない乳児例は強化された化学療

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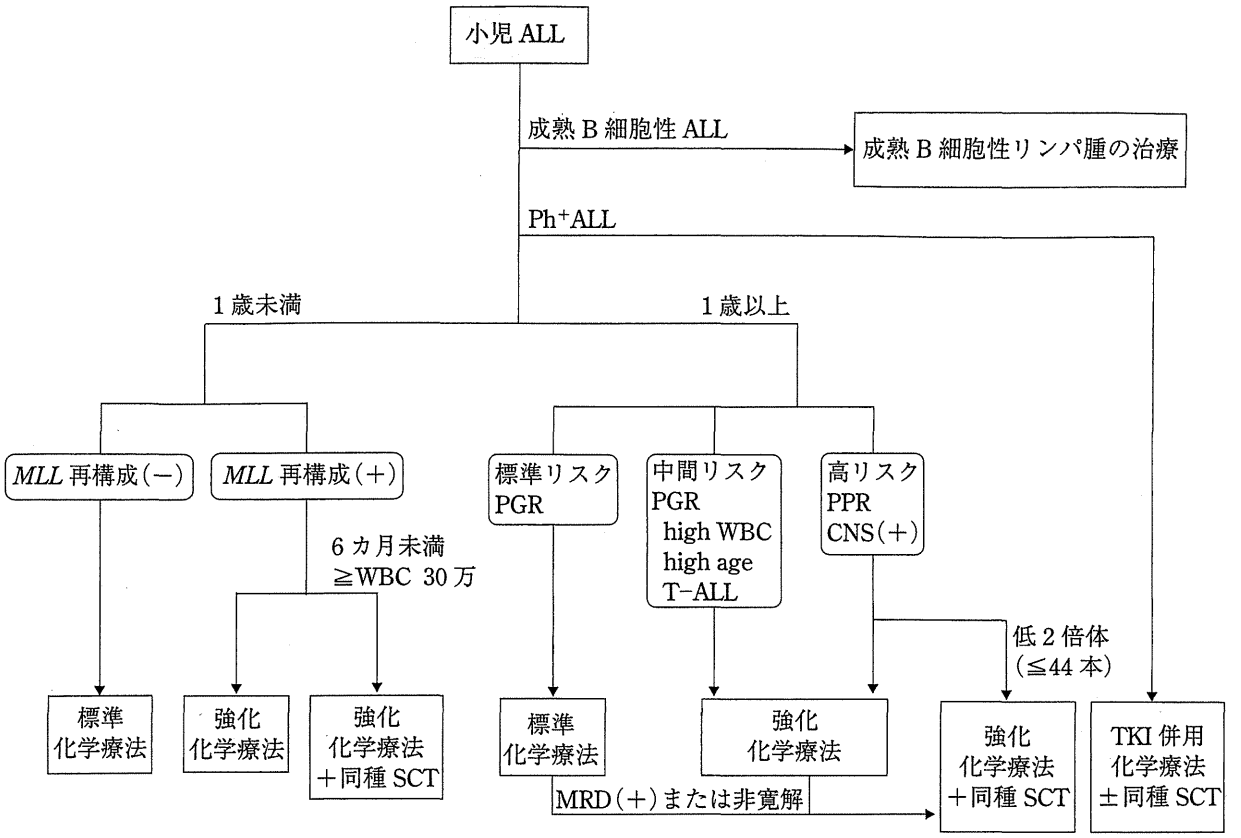

図 1 小児 ALL の治療選択アルゴリズム(小児白血病・リンパ腫の診療ガイドライン 2011 年版(文献[4])より引用)
PGR: prednisolone good responder, PPR: prednisolone poor responder.

法で 90 % 以上の長期寛解生存が期待できる. 一方で *MLL* 遺伝子再構成を伴う例は, ほとんどが CD10 陰性の B 前駆細胞性 ALL(BCP-ALL)であり, 同種 SCT を併用しても 5 年全生存率が 50 % 前後である[5]. また, 移植生存例の 50 % 以上で成長障害や晩期合併症を認める. 欧米の研究で *MLL* 陽性例の中でも予後不良因子(診断時月齢 6 カ月未満, 診断時白血球数 30 万/μL 以上)をもたない場合は化学療法単独で治療できる可能性が示唆されている.

1 歳以上の Ph 陰性 ALL のリスク分類は, 年齢, 初診時白血球数, 免疫学的マーカー, 染色体・遺伝子型, および初期治療反応性を考慮して 3 群に分類される. 更に, 寛解導入療法中および後の骨髄微小残存病変(MRD)の有無でリスクの変更や同種 SCT の適応判断が行われている. T 細胞性(T-)ALL は, 一般に高リスク群として強化された治療が行われるが, 特有の生物学的特徴を有し, メトトレキサート(MTX)の活性化代謝物が蓄積しにくく, 骨髄 MRD の動態が BCP-ALL と異なることや T-ALL に選択的に有効な薬剤が開発されたことから現在は独自の治療研究が行われている. また, 15 歳以上の ALL においても, 小児の治療レジメンの有用性が示されており, 最近の前向き研究で 35-45 歳まで実施可能とする報告がみられる.

2 小児 ALL の標準的治療戦略

小児 ALL の標準的治療骨格は, 寛解導入療法, 地固め療法, 中間維持療法(中枢神経系白血病予防治療), 後期強化療法(再寛解導入療法), 維持療法からなる[6].

1) 寛解導入療法

白血病の治療で第一に目指すのは完全寛解(CR)を得ることである. 通常 4 週間の治療を

行い，その過程でCRが得られる．通常，ビンクリスチン(VCR)4回，プレドニゾロン(PSL)28日間，L-アスパラギナーゼ(ASP)8-9回の3剤治療で軽度の骨髄抑制で90％以上のCR率が期待できるが，より深い寛解を得ることで再発率の低下につなげられるため，骨髄抑制の強いダウノルビシン(DNR)を再発リスクが高い(HR)患者には4回，再発リスクが高くない標準リスク(SR)患者には2回投与される．米英の研究グループでは，低リスク(LR)患者にダウノルビシン(DNR)を用いず，3剤での寛解導入療法が行われる．また，プレドニゾロン(PSL)の代わりにデキサメタゾン(DEX)を用いた場合，より高いCR率が期待できるが，感染症が増えるため全生存率に差がないとする報告が多い．しかし，T-ALLでDEX群がPSL群よりも全生存率が有意に良好であったとの報告がある．ASPは，通常*E. coli*由来製剤が用いられるが，半減期が短いため頻回投与が必要であり，アレルギーが約20％に認められることから代替薬の開発が待たれる．

Burkitt白血病は，細胞回転が速く早期に薬剤耐性化しやすいため，通常のALLの寛解導入療法を行うと早期再発する．リンパ腫治療に準じてVCR，PSL，ドキソルビシン(DOX)に頻回シクロホスファミド(CPA)，大量MTXを併用して寛解導入を図る．

2) 地固め療法

地固め療法は，通常，寛解導入療法薬と交差耐性のない異なる薬剤の組み合わせで3-4週間行う．CPA，6-メルカプトプリン(6MP)，シタラビン(CA)が用いられる．エトポシド(ETOP)は，HR患者でしばしば用いられるが，二次性白血病のリスクを回避するためSR患者では使われない．また，HR患者でASPによる治療強化でEFSの改善が報告されている．この時期はMTX髄腔内注入(髄注)によるCNS治療を強化する時期でもある．

3) 中枢神経系(CNS)強化療法

もともと後述の再寛解導入療法までの維持療法期間であり，MTXと6MPが用いられるが，この時期をCNS強化治療相としてMTXの中等量～大量(HD)療法と髄注療法が行われる．米国COGでは，HR患者に対し中等量MTXにVCR，ASPを加えて強化したaugmentedレジメンを考案し，その有用性が示された．更にHD-MTXと中等量MTXの比較試験でHD-MTXの有用性が確立された[7]．また，以前は予防的頭蓋放射線照射(CRT)が行われていたが，髄注の強化や全身化学療法の強化によりCRT適応範囲は，CNS白血病や白血球数10万/μLのT-ALLに限定される．海外では，予防的CRTを全廃しても5年EFS 86％の極めて良好な成績が報告されている[8]．

4) 後期強化療法(再寛解導入療法)

寛解導入療法を寛解後数カ月以内に繰り返すことで治療成績が向上することが，多くの比較試験で確認されている．この治療相ではDOXやDEXが比較的安全に投与される．我が国では，心毒性の低減を目的にピラルビシン(THP)も用いられる．DEXは骨壊死のリスクを高めるため，10歳以上で間欠投与が推奨される[9]．再発リスクが中間(IR)のALLで2回の後期強化療法の有用性が示されている．VCRとDEX(VD)のパルス強化治療では治療成績の向上が得られないことから，ASPとDOXが加えられたことによる効果が考えられる．

5) 維持療法

維持療法の基本は，週1回のMTXと6MP連日経口投与である．治療中は白血球数3,000/μL未満を維持することが推奨される．朝よりも夕方に服用する方が効果的であり，6MPはキサンチン酸化酵素を多く含む乳製品の同時摂取を避ける．維持療法中にしばしば肝酵素の上昇が認められるが，治療終了後に速やかな改善が期待でき，肝酵素の上昇が予後良好因子との報告もあるため，他の原因がないかぎりMTXや6MPの減量中止を行わない．維持療法中のVCR+PSLまたはVCR+DEXのパルス療法は初期治療が弱い場合は有用であるが，初期治療が強力な場合の評価は定まっていない．寛解後の治療期間は，通常2-3年である．比較的弱い初期治療の場合は維持療法期間に性差があり，男児で3年間の維持療法が有用とされる．

6）造血幹細胞移植(SCT)の適応

一般に，SCTは化学療法よりも晩期合併症が高頻度に起こるため，適応は難治例に限られる．化学療法での長期生存の見込みが40％未満の場合に同種SCTが考慮される．小児ALLにおける第一寛解期での同種SCTの適応は，予後不良な生物学的因子をもつ例(染色体数44本未満，Ph陽性，初期治療反応不良なMLL-AF4，t(17;19))，寛解導入不能例，および，12週のMRD陽性例であるが，ドナーの有無，年齢，短期および長期の合併症リスクや再発後の救済の可能性について個別に検討が必要である．移植前処置として，全身放射線照射(TBI)が有用であり，CPAおよびETOPの大量療法，または，メルファラン大量療法と組み合わせて行われる．晩期合併症が多い高線量TBIの回避が課題である．

3 再発ALLの治療選択

小児ALLの治療成績が向上したとはいえ，再発率は20％に及び，再発ALLは，第3の小児血液がんといわれている．再発ALLもリスク分類による層別化治療が行われ，再発時期(超早期，早期，晩期)と再発部位(髄外単独，骨髄と髄外の複合，骨髄単独)，T-ALLか否かで予後が異なり，3つのリスク(SR・IR・HR)に分類される[4]．再発時期が早期であるほど予後不良であり，T-ALLの再発例はBCP-ALLよりも予後は悪い．SRとIRについては，初回治療に使われた薬剤の感受性が認められるため，寛解導入療法は，初発ALLと同様の化学療法で90％以上の寛解導入率が期待できる．一方，治療中もしくはT-ALLの骨髄再発例であるHRは，第二寛解導入率が低く，新薬の登場が待たれる．寛解後の治療は，第二寛解期同種SCTの成績が良好な我が国ではSCTが選択される場合が多い．しかし，寛解後のMRD陰性例は化学療法＋CRTで良好な成績が期待できることがBFM(Berlin-Frankfurt-Münster)グループから報告されており，その検証が待たれる．

4 小児ALL治療薬開発の展望

小児ALL治療に求められる薬剤は，難治例に有効な新規薬剤だけでなく，長期的影響を鑑みた安全な薬剤である．喫緊に臨床導入が期待される薬剤を紹介する．

1）最近の新薬

(1) ネララビンは，プリン拮抗薬であり，T細胞性腫瘍に特異的効果が期待され，2007年に承認された．神経毒性が懸念されるものの骨髄抑制をはじめ臓器毒性が比較的軽度であり，併用療法での安全性も確認されており，高リスクT-ALLでの有用性が期待される[10]．

(2) クロファラビン(CLO)もプリン拮抗薬であり，再発，難治性ALLの適応症で2013年6月に承認された．欧米において難治性小児ALLに対してCLO＋CPA＋ETOPやCLO＋Peg-ASPで有用性が報告されている[11]．

2）臨床試験中の分子標的薬

(1) Ph陽性ALLにおいてABLキナーゼ阻害薬であるイマチニブを従来の化学療法に長期に併用することで安全に治療成績の向上が達成された．今後，ダサチニブなどの第二世代ABLキナーゼ阻害薬の併用で更なる成績向上が期待される．また，FLT3遺伝子異常を高頻度に認める乳児白血病に対してFLT3キナーゼ阻害薬の開発が米国で進められている．

(2) ボルテゾミブは，難治性または再発した多発性骨髄腫を適応症として市販されているプロテアソーム阻害薬であり，単剤では再発白血病に効果はないが，DEX，VCR，ASP，DOXとの併用で相乗相加効果が期待でき，再発小児ALLで有用性が示されている[12]．

3）毒性を軽減した改良型薬剤

(1) ペグアスパラギナーゼは，*E. coli*由来ASPの半減期の延長と免疫原性の減少が図られた製剤で欧米のALL標準治療薬になっている．

(2) エルイナーゼは，*Erwinia chrysanthemi*菌由来のASP製剤で，*E. coli*由来製剤にアレルギーを認めた場合に用いる代替薬である．欧米各国で認可されており，我が国でも現在治験中である．

(3) リポ化ダウノルビシン(ダウノキソーム)は，我が国では未承認薬だが，心毒性軽減を目的に開発され，更に組織集積性による効果の増大が期待される薬剤である．

(4) リポ化ビンクリスチンは，未承認薬だが，VCRの投与量や薬物動態の限界を克服するために開発され，2.25 mg/m^{2}を上限なしで毎週投与が可能となり，難治例での有用性が示唆されている[13]．

4) 抗体製剤[14]

小児ALLで有用性が確立した抗体製剤はないが，成人B細胞性腫瘍で開発が進められており，いずれ小児例での検証が待たれる．

(1) 抗体単体の製剤：リツキシマブは，毒性を増加させることなく成人B細胞性ALLでの有用性が確立している．オファツムマブは，作用機序の異なる抗CD20抗体製剤であり，再発または難治性のCD20陽性の慢性リンパ性白血病で承認が得られている．抗CD22抗体製剤のエプラツズマブや抗CD52抗体製剤のアレムツズマブも治験中であり，B細胞性腫瘍への応用が期待される．

(2) 薬物や毒素を抱合した抗体製剤：イノツズマブ・オゾガマイシンは，カリケアマイシンを結合させた抗CD22抗体であり，米国の小児および成人ALLに対する臨床試験で単剤での有効性が確認されている．また，抗CD19抗体とメイタンシノイドの複合体であるSAR3419やシュードモナス外毒素を結合した抗CD22抗体製剤BL22の改良型のモキセツモマブも注目される．

(3) 改変型抗体製剤：ブリナツモマブは，二重特異性T細胞結びつけ(bispecific T-cell engager: BiTE)抗体であり，CD19抗体を介してT細胞をALL細胞に結合させる．成人ALLで有望な臨床効果が得られている．MOR208(XmAb5574)は，Fc部分を改変したヒト化抗CD19モノクローナル抗体でB細胞性腫瘍での効果が期待されている．

5) 気になる適応外薬

(1) テムシロリムスは，哺乳類ラパマイシン標的タンパク質(mTOR)阻害薬で進行性腎細胞癌の効能・効果で市販されているが，ヒストン脱アセチル化酵素阻害薬との併用で相乗的にMYCタンパクを阻害して抗腫瘍効果を発揮することが知られている．

(2) エリブリンは，日本生まれの新規微小管阻害薬で手術不能・再発乳がんの効能・効果で市販されているが，米国の小児がん前臨床試験でALLに高感受性が認められており，臨床導入が期待される[15]．

おわりに

網羅的な遺伝子解析によってALLの様々な遺伝子異常が明らかにされ，新たな予後因子および治療の分子標的として注目されている．今後は，毒性の軽減を目指した薬剤開発とともに，抗体製剤や分子病態の解明に基づく分子標的薬の開発が進み，より安全でリスク/病型特異的な治療戦略が追究されていくものと思われる．

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