80.4 %. 2 patients had CR, 17 patients had PR, and 18 patients had SD.

Figure 1 shows the OS of the 46 enrolled patients. The median OS was 17.4 months (95 % CI, 14.1 to 21.6), with 1-year survival rate of 67.4 % (95 % CI, 52.0 to 80.5). The median PFS was 7.5 months (Fig. 2).

Toxicity Major grade 3 and 4 toxicities are summarized in Table 2. Myelosuppression was the most common toxicity of grade 3/4, with neutropenia occurring in 13 (28.3 %) patients, anemia in 8 (17.4 %) patients, and thrombocytopenia in 6 (13.0 %) patients. Severe nonhematologic toxicities were uncommon in this study. There was no treatment-related death.

Discussion

Diagnosis of metastatic CUP has long been considered synonymous with poor prognosis. Combination regimens containing a taxane and a platinum agent have been most extensively studied [3–7]. In practical settings, empiric chemotherapy is generally administered to patients with CUP. However, empiric chemotherapy, for example, paclitaxel and carboplatin, is not expected to be efficacious in patients with several carcinomas. Moreover, this regimen is believed to be poorly effective when the primary site is colorectal, renal, pancreatic, prostatic, or hepatic. In this respect, S-1 is considered to have broad spectrum of clinical activity in solid tumors. In the present study, we demonstrated that CDDP plus S-1 combination chemotherapy achieved a response rate of 41.3 %, median MST of 17.4 months, and 1-year survival rate of 67 %.

Table 2 Treatment-Related Toxicity (N=46)

Toxicity	No. of patients (%)	
	Grade 3	Grade 4
Hematologic		
Leukopenia	4 (8.7)	1 (2.2)
Neutropenia	8 (17.4)	5 (10.9)
Anemia	5 (10.9)	3 (6.5)
Thrombocytopenia	4 (8.7)	2 (4.3)
Nonhematologic		
Neutoropenic fever	1 (2.2)	0
Anorexia	4 (8.7)	0
Nausea/vomiting	2 (4.3)	0
Fatigue	1 (2.2)	–
Diarrhea	1 (2.2)	0

However, careful attention should be paid to the interpretation of our promising results. Importantly, patient selection may have influenced the study outcomes. Poor prognostic factors—including male gender, PS score greater than 1, high number of metastatic sites, presence of liver metastases, elevated serum alkaline phosphatase, elevated lactate dehydrogenase (LDH), and low serum albumin—have been identified in CUP patients. In our study, the majority (89.1 %) of the patients had good PS scores of 0–1, and 30 % of the patients was squamous cell carcinoma, whereas a small percentage (10.9 %) of patients had liver metastases, 39.1 % had high LDH levels, and 39.1 % had nodal disease only. These favorable prognostic features of enrolled patients may contribute to good clinical outcome observed in this study.

Recently, various targeted agents have been included in the treatment of several common solid tumors [18, 19]. As development of molecular target agents advances, prognostics may be improved by classifying cases with CUP into subgroups according to the expression of specific biomarkers.

On the other hand, molecular profiling assays, which may assist in the identification of the tissue of origin, have attracted increasing attention. Indeed, the development molecular technologies that allow tumor gene expression profiling provides an opportunity for improved diagnosis of patients with CUP [20, 21]. Clinical trials are currently being conducted to examine the efficacy of therapy directed based on the molecular profiling assay diagnosis of patients with CUP.

In our study, the treatment-related toxicity of the S-1/CDDP regimen was mild in the majority of the patients. However, we should note that the recommend dose of S-1 may be different between Japanese and Western patients. In the FLAGS trial (Multicenter Phase III Comparison of Cisplatin/S-1 with Cisplatin/Infusional Fluorouracil in Advanced Gastric or Gastroesophageal Adenocarcinoma Study), patients in the CDDP plus S-1 arm received S-1 at 50 mg/m^2/day [22] . This dose has been considered the maximum-tolerated dose in combination with CDDP in Western patients. On the other hand, we and other Japanese trial [23, 24] have shown that Japanese patients tolerate well S-1 at 80 mg/m^2/day. This difference in tolerance to S-1 has been suggested to be likely related to polymorphic differences in the key *CYP2A6* gene [25]. Thus, ethnic differences should be taken into account before introduction of S-1 plus CDDP combination therapy in patients with CUP.

In conclusion, this nonrandomized phase II trial demonstrated the efficacy and safety of using S-1 in combination with CDDP as the first-line treatment for patients with CUP.

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Disclosure of potential conflicts of interest All authors declare no conflicts of interest.

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Practical Use of Gemcitabine and Cisplatin Combination Therapy as First-Line Treatment for Japanese Patients with Advanced Biliary Tract Cancer*

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ABSTRACT

Gemcitabine and cisplatin combination therapy (GC) is accepted as a standard treatment for advanced biliary tract cancer (BTC). However, little information is available regarding such treatment in the clinical practice setting in Japan. We retrospectively examined the clinical data of patients with unresectable or recurrent BTC who received GC as first-line treatment. The regimen consisted of cisplatin (25 mg/m^2) and gemcitabine (1000 mg/m^2) administered intravenously on days 1 and 8 of repeated 3-week cycles. Twenty patients were analyzed. A total of 148 cycles of GC was administered, with a median of 8 and a range of 1 to 18 cycles. Treatment delay and dose reduction were noted in 35 (24%) and 41 (28%) of the 148 cycles, respectively. The major adverse events of grade 3 or 4 included neutropenia (50%), leukopenia (45%), anemia (30%), and thrombocytopenia (15%). Nonhematologic toxicities included nausea (10%), appetite loss (10%), and fatigue (10%). Median progression-free and overall survival times were 6.9 and 12.3 months, respectively. Gallbladder cancer showed a significantly higher response rate than did other types of BTC (chi-squaretest, $P = 0.002$). GC was thus effective and well tolerated as first-line chemotherapy for Japanese patients with advanced BTC in the clinical practice setting.

Keywords: Gemcitabine; Cisplatin; Chemotherapy; Biliary Tract Cancer

1. Introduction

Biliary tract cancer (BTC) is a rare type of cancer worldwide, but it is more common in East Asia and Latin America than in other regions [1]. In Japan, BTC is the sixth leading cause of death from cancer [2] and its prevalence is increasing. Although the most effective treatment for localized disease is surgery, most cases of BTC are diagnosed as advanced and inoperable, despite substantial progress in diagnostic imaging. Outcomes are extremely poor in such patients, with a median survival time of 2.5 months with best supportive care [3].

Gemcitabine has shown antitumor activity in patients with BTC, as revealed by the results of predominantly phase II studies [4-6], and this drug is generally used in the palliative setting, yielding a median survival time of 6 to 9 months. Cisplatin is a key anticancer agent for solid tumors and is widely administered in combination chemotherapy. Gemcitabine and cisplatin combination therapy (GC) has shown promising antitumor efficacy in several phase II studies with BTC patients [7-12]. Given these results, a phase III trial comparing GC with gemcitabine alone was conductedfor locally advanced or metastatic BTC in the United Kingdom (ABC-02 study). A total of 410 patients were randomly assigned to receive gemcitabine (1000 mg/m^2 on days 1, 8, and 15 of a 4-week cycle) or GC (1000 mg/m^{2}and 25 mg/m^2, respectively, on days 1 and 8 of a 3-week cycle). The median overall survival (OS)was significantly better forthe patients receiving GC than for those receiving gemcitabine alone (11.7 versus 8.1 months; hazard ratio [HR] of 0.64, with a 95% confidence interval [CI] of 0.52 to 0.80; $P <$

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0.001).The median progression-free survival (PFS) was also significantly longer for the GC group than for the gemcitabine group (8.0 versus 5.0 months; HR of 0.63, with a 95% CI of 0.51 to 0.77; $P < 0.001$) [13]. On the basis of the results of the ABC-02 study, GC was recognized as the standard of care for the treatment of advanced BTC.A randomized phase II study comparing GC with gemcitabine alone was also performed for locally advanced or metastatic BTC in Japan (BT22 study), with the same treatment dose and scheduleas adopted in the ABC-02 study. Overall, 84 patients were randomized to receive either GC or gemcitabine alone. The 1-year survival rate, which was the primary endpoint of the study, was higher in the GC group than in the gemcitabine group (39.0 versus 31.9%) [14]. The findings of the ABC-02 and BT22 studies have thus resulted in GC becoming accepted as a standard treatment for patients with BTC in Japan. To date, however, information regarding the safety and efficacy of GC in Japanese individuals with BTC has been limited to that obtained from 42 patients in the BT 22 study. The safety and efficacy of GC in the clinical practice setting have thus remained uncertain. We now report our experience with GC for Japanese patients with BTC in the clinical practice setting.

2. Methods

2.1. Eligibility Criteria

We reviewed the cases in our database and retrospectively examined the clinical data of patients with unresectable or recurrent BTC who received GC as the first-line treatment. Patients were eligible if they had: 1) pathologically or radiographically confirmed BTC; 2) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; and 3) adequate bone marrow function (white blood cell count of >3000/mm^3, hemoglobin content of >9.0 g/dl, and a platelet count of >100,000/mm^3), liver function (total serum bilirubin concentration of less than three times the upper limit of normal [ULN], and serum aspartate and alanine transaminase levels of less than five times the ULN), and renal function (serum creatinine concentration of <1.2 mg/dl and creatinine clearance of >50 ml/min). In patients with obstructive jaundice, the total serum bilirubin concentration was required to be less than three times the ULN after biliary drainage. Written informed consent was obtained from each patient prior to treatment administration.

2.2. Treatment Schedule

GC was administered mostly on an outpatient basis. Gemcitabine was given intravenously (1000 mg/m^2) over 30 min and cisplatin was administered intravenously (25 mg/m^2) over 120 min on days 1 and 8 of a 3-week cycle. Treatment was continued until disease progression, the occurrence of unacceptable toxicity, or patient refusal. We adopted the following general administration criteria for GC: a neutrophil count of ≥1500/mm^3, a platelet count of ≥75,000/mm^3, a serum total bilirubin concentration of ≤2.5 mg/dl, a serum creatinine level of ≤1.5 mg/dl, and other nonhematologic toxicity of grade 1 or less. Administration of gemcitabine alone after discontinuation of GC was allowed at the discretion of the physician, whereas administration of cisplatin alone was not allowed. Antiemetic prophylaxis with 5-HT$_3$ serotonin receptor antagonists plus dexamethasone was administered in all cases. A neurokinin-1 receptor antagonist was used at the physician's discretion.

2.3. Toxicity Evaluation

All adverse events were reviewed based on medical records and evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The highest toxicity grade for each patient in all cycles of chemotherapy was used for toxicity analysis.

2.4. Efficacy Measures

The efficacy end points were tumor response, PFS, and OS. Tumor assessment by computed tomography of the abdomen and chest was performed at baseline and after two cycles of chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PFS was defined as the time from enrollment to the date of confirmation of progressive disease or of death from any cause, whichever occurred first. OS was defined as the time from registration until death from any cause. Patients not known to have died or to have developed progressive disease were censored at the date of the last progression-free assessment.

2.5. Statistical Analysis

Survival curves were constructed by the Kaplan-Meier method and were compared with the log-rank test. Differences in tumor response were evaluated with the chi-square test. Statistical analysis was performed with the use of IBM SPSS statistics software version 20. A P value of <0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

The characteristics of the 20 enrolled patients are listed in **Table 1**. The median age of the patients was 64.5 years, with similar numbers of men and women. Six individuals were 70 years of age or older. Five patients

Table 1. Patient characteristics.

Characteristic	No. of patients (%)
Sex	
Male	11 (55%)
Female	9 (45%)
Age (years)	
Median	64.5
Range	44 - 76
Performance Status	
0/1/2	7/11/2 (35%/55%/10%)
Primary tumor site	
Extrahepatic bile duct	6 (30%)
Intrahepatic bile duct	8 (40%)
Gallbladder	6 (30%)
Metastatic sites	
Regional lymph nodes	17 (85%)
Distant lymph nodes	13 (65%)
Liver	15 (75%)
Peritoneum	2 (10%)
Lung	2 (10%)
Other	4 (20%)
Initial onset or recurrence	
Initial onset	15 (75%)
Recurrence after surgery	5 (25%)
Histological type	
Adenocarcinoma	14 (70%)
Adenosquamous carcinoma	1 (5%)
Cholangiocarcinoma	1 (5%)
Not obtainable	4 (20%)
Disease stage (extrahepatic bile duct cancer, gallbladder cancer)	
IIA	0 (0%)
IIB	1[a] (5%)
III	1 (5%)
IV	6 (30%)
Reccurence after surgery	4 (20%)
Disease stage (intrahepatic bile duct cancer)	
II	1[a] (5%)
III	0 (0%)
IVA	2 (10%)
IVB	4 (20%)
Reccurence after surgery	1 (5%)
Biliary drainage	
Yes	2 (10%)
No	18 (90%)

[a]Patients were diagnosed as having unresectable disease with marked regional node metastases involving the proper hepatic artery or main portal vein.

(25%) had recurrent metastatic disease after surgical resection, and 15 (75%) had unresectable metastatic disease at the initial diagnosis. Tumor specimens were obtained from 16 individuals, including 14 patients with adenocarcinoma, one patient with adenosquamous carcinoma, and one patient with cholangiocarcinoma. The primary tumor sites included the gallbladder in six patients (30%), the intrahepatic bile duct in eight patients (40%), and the extrahepatic bile duct in six patients (30%). Regional lymph nodes were the most common metastatic site, followed by the liver and distant lymph nodes.

3.2. Treatment Delivery

The data for treatment delivery are summarized in **Table 2**. Seventeen patients (85%) required a treatment delay and eight patients (40%) required dose reduction. A total of 148 cycles of GC was administered, with a median of 8 and a range of 1 to 18 cycles per patient. Treatment delays and dose reductions were noted in 35 (24%) and 41 (28%) of the 148 cycles, respectively. Most treatment delays (24 out of 35 cycles) were due to hematologictoxicity that persisted for up to 7 days;the remaining 11 cycles were delayed for >2 weeks (15 to 70 days) be

Table 2. Summary of treatment delivery.

Total treatment cycles	148
Median no. of cycles (range)	8 (1 - 18)
Treatment delay	
Cycles (%)	35 (24%)
Reasons (cycles)	Neutropenia (19)
	Fever (5)
	Fatigue (3)
	Anemia (2)
	Patient's request (2)
	Platelet count decreased (2)
	Serum creatinine level increased (1)
	Febrile neutropenia (1)
Dose reduction	
Cycles (%)	41 (28%)
Reasons (cycles)	Neutropenia (25)
	Platelet count decreased (8)
	Fatigue (4)
	Febrile neutropenia (4)

cause of the development of prolonged neutropenia (6 cycles), prolonged thrombocytopenia (2 cycles), prolonged anemia with refusal of blood transfusion (1 cycle), febrile neutropenia of grade 3 (1 cycle), or fever of grade 1 (1 cycle). The reasons for dose reduction included the development ofneutropenia (25 of 41 cycles), thrombocytopenia (8 cycles), fatigue (4 cycles), or febrile neutropenia (4 cycles).Reasons for discontinuation of treatment included radiologically determined progressive disease (15 cases), treatment refusal (2 cases), and surgery with curative intent (1 case).

3.3. Toxicity

Major adverse events during the entire period are presented in **Table 3**. No treatment-related deaths occurred. The major adverse events of grade 3 or 4 included neutropenia (50%), leukopenia (45%), anemia (30%), and thrombocytopenia (15%). Although neutropenia was the most common hematologic toxicity, febrile neutropenia of grade 3 was observed in only one case (5%). With regard to nonhematologic toxicity, no toxicities of grade 4 were observed and those of grade 3 included nausea (10%), appetite loss (10%), and fatigue (10%), all of which were manageable. Biliary tract infection of grade 3 was seen in one patient (5%), but it resolved within a week of antibiotic therapy.

Table 3. Treatment-related toxicities (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events) in the 20 study subjects.

	No. of patients (n = 20)			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	1	1	8	1
Neutropenia	1	0	6	4
Febrile neutropenia	-	-	1	0
Thrombocytopenia	8	4	2	1
Anemia	5	6	6	0
Serum creatinine increased	2	0	0	0
Constipation	12	4	0	0
Nausea	1	0	2	0
Appetite loss	8	4	2	0
Fatigue	7	4	2	-
Biliary tract infection	-	-	1	0
Vomiting	2	1	0	0
Fever	3	0	0	0
Stomatitis	3	0	0	0
Peripheral sensory neuropathy	2	0	0	0

3.4. Response

The chemotherapeutic responses are summarized in **Table 4**. All patients but one were assessable for tumor response. Although no individual achieved a complete response, six patients achieved a partial response, giving a best overall response rate of 30% (95% CI, 15 to 52%). Ten patients (50%) showed stable disease, and the remaining three patients (15%) had progressive disease. Five of the six responders had gallbladder cancer (GBC). Response differed significantly (chi-square test, P = 0.002) between patients with GBC (n = 6) and those with other types of BTC (n = 14).

3.5. Survival

At the time of analysis, 18 patients had died of their disease. With a median potential follow-up time of 12.5 months, median OS and median PFS were 12.3 months and 6.9 months, respectively (**Figure 1**). Neither median OS nor median PFS differed significantly between patients with GBC and those with other forms of BTC.

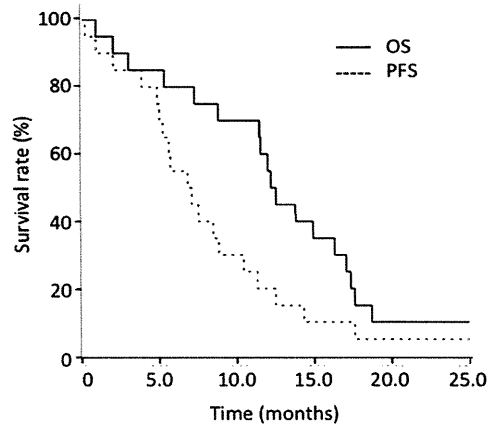

Figure 1. Kaplan-Meier analysis of OS and PFS for all patients (n = 20) from the onset of chemotherapy.

Table 4. Chemotherapeutic response according to tumor site.

Tumor site	No. of patients				
	CR	PR	SD	PD	NE
GBC	0	5*	1	0	0
Other BTCs	0	1	9	3	1
All (%)	0 (0%)	6 (30%)	10 (50%)	3 (15%)	1 (5%)

Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, GBC = gall bladder cancer, BTC = biliary tract cancer. *P = 0.002 versus the corresponding value for other BTCs (chi-square test).

Second-line chemotherapy was administered to 12 patients (60%), all of whomreceived S-1 monotherapy.

4. Discussion

GC is now accepted worldwide as a standard regimen for first-line chemotherapy in patients with advanced BTC, largely on the basis of the results of the first large phase III study (ABC-02) showing the superiority of GC compared with gemcitabine monotherapy for this condition [13]. Although gemcitabine combined with oxaliplatin or capecitabine has shown promising efficacy for patients with BTC in single-arm phase II trials, yielding a response rate of ~50% and OS of ~14.0 months [15], these treatments have not been evaluated in randomized phase III trials in comparison with gemcitabine alone. The safety and efficacy of GC for Japanese patients with BTC were also recently demonstrated in a randomized phase II trial (BT22) [14].GC was thus approved in February 2012 for the treatment of advanced BTC in Japan. Given the widespread adoption of GC for the treatment of advanced BTC, further information on its toxicity and treatment delivery characteristics in the clinical practice setting is of value.

Most toxicities observed in our study were hematologic in nature. The incidence ofleukopenia (45%) or neutropenia (50%) of grade 3 or 4 wassimilar to that observed in theprevious Japanese BT22 study (29.3 and 56.1%, respectively) [14] but washigher than that apparent among Caucasiansin the ABC-02 study (15.7 and 25.3%, respectively) [13], consistent with the notion of anethnic difference in the hematologic toxicity of chemotherapy between Japanese and Caucasian patients with BTC [16]. We further investigated the effect of dose reduction on efficacy. Overall, 40% (8/20) of patients required a dose reduction, mostly as a result of hematologic toxicity. Among the patients who underwent a dose reduction, the median PFS and response rate were 5.8 months and 12.5% (1 out of 8 patients), respectively. In contrast, a median PFS of 8.5 months and response rate of 41.7% (5 out of 12 patients) were apparent for the individuals who received the starting dose of GC throughout the treatment period. Nonhematologic toxicity was acceptable in the present study, with frequent adverse events including fatigue and gastrointestinal manifestations, both of which were clinically reversible. The overall profile and frequency of nonhematologic toxicities in our analysis are consistent with those observed in previous trials [13,14].

Cisplatin is one of the most effective chemotherapeutic agents for the treatment of many types of solid tumors, but its administration is limited over the long term because of its cumulative toxicity, including neurological toxicity. Such problems occur even if cisplatin is administered at a low dose. In the ABC-02 study, GC was delivered for up to a maximum of eight cycles, corresponding to a total cisplatin dose of 400 mg/m^2 [13]. GC was continued for up to a maximum of 16 cycles in the BT22 study [14]. However, little has been known of the safety or efficacy of GC in patients receiving a total cumulative dose of cisplatin of >400 mg/m^2. In the present study, cisplatin was administered at a median total dose of 347.5 mg/m^2, with a range of 25 to 550 mg/m^2. Four of the 20 patients received cisplatin at >400 mg/m^2, and these individuals did not experience significant toxicity other than peripheral neuropathy of grade 1. Further studies are needed, however, to determine the optimal total dosage of cisplatin for treatment of BTC with GC.

Although patients with GBC showed a significantly higher response rate compared with those with other types of BTC in the present study, this finding is not particular to GC. Subgroup analysis of the ABC-02 study revealed a higher response rate for GBC than for other forms of BTC in both the gemcitabine arm (21.4 versus 11.7%) and the GC arm (37.7 versus 18.0%) [13]. Furthermore, a previous pooled analysis of clinical trials revealed that GBC showed a higher response rate to drugs such as fluoropyrimidines, gemcitabine, and platinum compounds administered as single agents or in combination therapy [17]. These findings may indicate that BTC comprises a heterogeneous group of carcinomas that can be classified crudely as GBC or others. Indeed, recent studies have suggested that GBC and other forms of BTC should be considered as distinct diseases with different clinicopathologic characteristics [18-20].

In summary, our results suggest that GC is effective and well tolerated in Japanese patients with advanced BTC even in the clinical practice setting. Most toxicities observed in our study were hematologic, with such toxicities being a major cause of both dose reduction and treatment delay. Such characterization of GC is important for the optimal treatment of patients with BTC in clinical practice.

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ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

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ABSTRACT

BACKGROUND

In single-group studies, chromosomal rearrangements of the anaplastic lymphoma kinase gene (*ALK*) have been associated with marked clinical responses to crizotinib, an oral tyrosine kinase inhibitor targeting ALK. Whether crizotinib is superior to standard chemotherapy with respect to efficacy is unknown.

METHODS

We conducted a phase 3, open-label trial comparing crizotinib with chemotherapy in 347 patients with locally advanced or metastatic *ALK*-positive lung cancer who had received one prior platinum-based regimen. Patients were randomly assigned to receive oral treatment with crizotinib (250 mg) twice daily or intravenous chemotherapy with either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks. Patients in the chemotherapy group who had disease progression were permitted to cross over to crizotinib as part of a separate study. The primary end point was progression-free survival.

RESULTS

The median progression-free survival was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (hazard ratio for progression or death with crizotinib, 0.49; 95% confidence interval [CI], 0.37 to 0.64; P<0.001). The response rates were 65% (95% CI, 58 to 72) with crizotinib, as compared with 20% (95% CI, 14 to 26) with chemotherapy (P<0.001). An interim analysis of overall survival showed no significant improvement with crizotinib as compared with chemotherapy (hazard ratio for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; P=0.54). Common adverse events associated with crizotinib were visual disorder, gastrointestinal side effects, and elevated liver aminotransferase levels, whereas common adverse events with chemotherapy were fatigue, alopecia, and dyspnea. Patients reported greater reductions in symptoms of lung cancer and greater improvement in global quality of life with crizotinib than with chemotherapy.

CONCLUSIONS

Crizotinib is superior to standard chemotherapy in patients with previously treated, advanced non–small-cell lung cancer with *ALK* rearrangement. (Funded by Pfizer; ClinicalTrials.gov number, NCT00932893.)

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Anaplastic lymphoma kinase (ALK) is a validated tyrosine kinase target in several cancers, including non–small-cell lung cancer, anaplastic large-cell lymphoma, and pediatric neuroblastoma.[1-3] *ALK* rearrangements are found in approximately 5% of cases of non–small-cell lung cancer and define a distinct molecular subtype of lung cancer.[4-7] With an estimated 1.3 million new cases of non–small-cell lung cancer worldwide each year,[8] this translates into more than 60,000 patients with *ALK*-positive non–small-cell lung cancer annually.

Crizotinib is an oral small-molecule tyrosine kinase inhibitor targeting ALK, MET, and ROS1 tyrosine kinases.[1,9,10] In two single-group studies, crizotinib showed marked antitumor activity in patients with advanced *ALK*-positive non–small-cell lung cancer, with objective response rates of approximately 60% and a median progression-free survival of 8.1 months in one of the studies and 9.7 months in the other.[11,12] In contrast, standard single-agent chemotherapies in the general population of patients with non–small-cell lung cancer have been associated with response rates of 10% or lower and median progression-free survival of 2 to 3 months.[13-15]

To date, the activity of standard chemotherapy has not been established in *ALK*-positive non–small-cell lung cancer. Retrospective studies suggest that *ALK* rearrangements may be associated with enhanced sensitivity to pemetrexed-based chemotherapy, with durations of response similar to those observed with crizotinib.[16,17]

We conducted a randomized, controlled, open-label, phase 3 trial of crizotinib, as compared with standard chemotherapy in patients with advanced, previously treated *ALK*-positive non–small-cell lung cancer.

METHODS

PATIENTS

Patients were eligible for inclusion in the study if they had locally advanced or metastatic non–small-cell lung cancer that was positive for *ALK* rearrangements. *ALK* testing was performed centrally with the use of a break-apart fluorescence in situ hybridization assay, which has an analytic sensitivity of 100% (95% confidence interval [CI], 98 to 100) and specificity of 100% (95% CI, 97 to 100).[1] Other eligibility criteria included an age of at least 18 years, progressive disease after one prior platinum-based chemotherapy regimen, measurable disease as assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[18] and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (with 0 indicating that the patient is fully active, 1 that the patient is ambulatory but restricted in strenuous activity, and 2 that the patient is ambulatory and capable of self-care but is unable to work[19]). Patients with stable brain metastases that had been treated previously or were untreated and asymptomatic were eligible. All patients provided written informed consent.

STUDY OVERSIGHT

The protocol was approved by the institutional review board or independent ethics committee at each participating site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. The study was designed by the sponsor (Pfizer) together with the members of the PROFILE 1007 steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The sponsor collected the data and analyzed them in conjunction with the authors. The corresponding author wrote all the drafts of the manuscript. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. Editorial support was provided by a medical writer at ACUMED (New York), who was funded by the sponsor. The protocol and statistical analysis plan are available at NEJM.org.

STUDY DESIGN AND TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive oral crizotinib (250 mg twice daily) in a 3-week cycle or intravenous chemotherapy comprising either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks. Patients who were randomly assigned to chemotherapy received pemetrexed unless their prior chemotherapy regimen contained pemetrexed or unless their tumor had predominantly squamous-cell histologic features. Patients were stratified according to ECOG performance status (0 or 1 vs. 2), the presence or absence of brain metastases, and prior or no prior therapy with epidermal growth factor receptor (EGFR) kinase inhibitors.

The primary end point was progression-free