Phase II Study of Pemetrexed and Cisplatin, with Chest Radiotherapy Followed by Docetaxel in Patients with Stage III Non-small Cell Lung Cancer

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Background: Pemetrexed has emerged as one of the most active agents for the treatment of patients with advanced non-small cell lung cancer (NSCLC). We conducted a phase II study to assess the efficacy and feasibility of integrating pemetrexed in a concurrent therapy plan for patients with stage III NSCLC.

Methods: Patients with stage III NSCLC with performance status 0 to 1, adequate organ function including pulmonary function, and V20 less than 40% were eligible. Patients were treated with cisplatin 75 mg/m^2 (first five patients 60 mg/m^2) and pemetrexed 500 mg/m^2 every 21 days for three cycles with chest radiotherapy to 66 Gy. Patients then received three cycles of docetaxel 75 mg/m^2 every 21 days. Tumors were analyzed for Excision Repair Cross Complementation Group 1 and thymidylate synthase.

Results: Patient characteristics (N = 28) were median age, 60; males, 68%; stage IIIB, 64%; and squamous cell, 43%. Twenty-four patients (86%) completed all three cycles of cisplatin/pemetrexed. Of the 24 patients eligible for docetaxel, 21 (87%) received it. Grade 3/4 toxicities were neutropenia (39%), febrile neutropenia (14%), esophagitis (14%), and pneumonitis (4%). Median survival was 34 months, and 1-year survival was 66%. Survival was not significantly different in squamous and other histology patients. Tumor analysis in 16 patients showed that moderate/strong expression of thymidylate synthase was significantly associated with progression-free survival and overall survival.

Conclusion: Integrating pemetrexed in a concurrent therapy regimen for patients with stage III NSCLC is feasible and was associated with a median survival of 34 months.

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Approximately, 33% of patients with non-small cell lung cancer (NSCLC) have stage III disease at diagnosis. The accepted therapy for patients with unresectable stage III NSCLC is concurrent chemotherapy and chest radiotherapy (CRT).[1,2] This standard reflects the understanding that both local tumor and systemic micrometastases need to be treated. Nevertheless, it is challenging to combine some of the newer chemotherapy agents at full dose with CRT.[3–5] Therefore, the combination of cisplatin and etoposide is commonly used for the management of patients with stage III NSCLC because these agents can be combined with CRT at full doses. The Southwest Oncology Group (SWOG) developed a regimen of concurrent cisplatin/etoposide and CRT followed by docetaxel. In a phase II study, S9504, this regimen resulted in a median survival of 27 months.[6] Nevertheless, both local and distant control rates were suboptimal in this trial. Therefore, there is a need to explore alternative regimens.

Pemetrexed is a multitargeted antifolate, with thymidylate synthase (TS) as one of the primary targets. It was initially approved for the treatment of recurrent NSCLC[7,8] and subsequently received approval for front line and maintenance therapy for patients with advanced nonsquamous NSCLC.[9,10] Seiwert et al.[11] conducted a phase I study evaluating pemetrexed and carboplatin with CRT and found that it was feasible to combine pemetrexed/carboplatin at full dose with CRT.

On the basis of these results, we initiated a phase II study evaluating pemetrexed and cisplatin with CRT for the management of patients with stage III NSCLC. On the basis of S9504, we planned consolidation docetaxel after concurrent therapy.

METHODS

Eligibility

Eligibility criteria included stage IIIA or IIIB NSCLC (without malignant pleural effusion) according to the Amer-

ican Joint Committee on Cancer Staging (AJCC) and Union Internationale Contre le Cancer (UICC) sixth edition[12] performance status 0 to 1, forced expiratory volume in 1 second (FEV1) of 1 liter or more and pulmonary diffusion capacity of at least 50% of predicted, and adequate hematologic, hepatic, and renal functions. Patients had to have calculated total lung volume receiving 20 Gy (V20) ≤40%. The study was approved by the institutional review boards of Karmanos Cancer Institute and John D. Dingell VA Medical Center. All patients were required to provide signed informed consent.

Treatment

Patients received three cycles of cisplatin and pemetrexed 500 mg/m^2 on days 1, 22, and 43. The first five patients received cisplatin 60 mg/m^2 per cycle. The dose of cisplatin was escalated to 75 mg/m^2 per cycle for all the subsequent patients. Patients received vitamin B12, folic acid, dexamethasone, and antiemetics as indicated. On the day of each cycle, patients received hydration as considered necessary for cisplatin therapy. Treating physicians were encouraged to administer 1 liter of normal saline the day after each cycle of chemotherapy.

Patients received CRT starting within 24 hours of the first dose of chemotherapy. The initial field received 2 Gy/d for 5 weeks for a dose of 50 Gy. An additional radiation boost to the gross tumor volume was administered with 2 Gy/d for 16 Gy, for a total tumor dose of 66 Gy. Both computed tomography (CT) scans and positron emission tomography (PET)/CT scans established the target volume. The gross tumor volume was defined as the tumor, the ipsilateral hilum, and nodes positive on PET or mediastinal staging procedures, or nodes ≥1 cm short axis on CT scan. The clinical target volume included 2 to 3 mm radially and adjusted for motion as imaged on conventional simulators. Treatment planning was done, such that at no point along the spinal cord the radiation dose exceeded 50 Gy.

Patients without evidence of disease progression and patients who had recovered from the adverse effects of concurrent therapy were treated with three cycles of docetaxel at 75 mg/m^2 every 21 days, starting no earlier than 4 weeks after completion of concurrent therapy. All patients received either pegylated filgrastim or filgrastim after each cycle of docetaxel.

Treatment Modifications

This study used the National Cancer Institute Common Toxicity Criteria version 3.0 for adverse event reporting. A delay in starting second and third cycles of pemetrexed/cisplatin for a maximum of 2 weeks was allowed for recovery from any adverse effects. Doses of both were reduced by 20% for grade 4 hematologic toxicity or any nonhematologic toxicity that was ≥grade 3 in the prior cycle. A break in radiotherapy was allowed, but was not mandated, for severe esophagitis and/or grade 4 hematologic toxicity. A delay in starting second and third cycles of docetaxel for a maximum of 2 weeks was allowed for recovery of any adverse effects. Patients with grade 3/4 adverse events were required to have appropriate dose modifications for the next cycle.

Study Evaluation and Follow-Up

All patients had disease assessment with appropriate scans after completion of concurrent therapy and within 4 weeks after completing docetaxel. All surviving patients were required to undergo disease assessment at 1 year. PET/CT scans were required after completion of concurrent therapy and 1 month after completion of docetaxel. Patients enrolled at the VA medical center were excluded from follow-up PET scans.

Thymidylate Synthase and Excision Repair Cross Complementation Group 1 Expression

Immunohistochemistry analysis was performed using archival blocks from consenting patients by standard methodology.[13] In brief, 4 to 5 μm paraffin sections on frosted slides (Snowcoat X-tra, Surigpath, Richmond, IL) were dewaxed and rehydrated through a xylene-ethanol series, and endogenous peroxides were removed by incubation of the slides in 1.2% hydrogen peroxide in methanol. Antigen retrieval was done in citrate buffer pH 6.0 in the microwave. Slides were blocked with 10% goat serum in phosphate-buffered saline (PBS) for 1 hour and incubated with the primary antibodies over night at 4°C. The mouse monoclonal Excision Repair Cross Complementation Group 1 (ERCC1) antibody used was from Neomarkers (Freemont, CA; Ab-2, clone 8F1dilution 1:200) and the mouse monoclonal TS antibody used was from Abcam (Cambridge, MA; clone TS 106, dilution 1:50). Normal mouse immunoglobulins (St. Cruz Biotechnol., St. Cruz, CA) were used instead of primary antibodies to probe negative control sections. Slides were then washed with PBS for three times and probed with the SuperPicture horse raddish peroxidase conjugate secondary antibody (Invitrogen, Camarillo, CA) for 2 hours, washed with PBS, and developed with diaminobenzidine substrate (Invitrogen). The tissues were counterstained with Gill's hematoxylin solution (Fisher Scientific, Pittsburgh, PA), dehydrated, and coverslipped with Eukitt mounting solution (Sigma, St Louis, MO).

Protein expression and staining intensity were evaluated in a blinded fashion by two independent observers (A.M.B. and L.M.). Nuclear expression of ERCC1 and TS were evaluated using a semiquantitative scoring system of 0 to 3+ as reported by us earlier[14] (0 = no expression, 0.5 to 1+ = weak expression, 1.5 to 2.5+ = moderate expression, and 3+ = strong expression). Three independent experiments were performed and a mean generated of the resulting six scores by the two observers.

Statistical Methods

The primary objective of this study was to estimate the 1-year survival rate. Secondary endpoints were response rate, progression-free survival (PFS), and toxicity assessment. We hypothesized that the1-year survival proportion is 0.55 for such patients from our cancer center's referral population, based on 1999–2001 survival statistics from the Detroit Surveillance Epidemiology End Results registry. We wish to find sample evidence from the study that supported the conclusion that the true 1-year survival proportion is not less than 0.45. As this was among the first trials evaluating the

incorporation of pemetrexed in a regimen of concurrent therapy for a patient population that has potentially curable disease, our primary concern was to be certain that this regimen did not increase the potential of inferior survival. A sample size of 28 produces a one-sided 85% lower-limit Wilson's confidence interval with the lower bound greater than 0.45. A statistical monitoring plan for toxicity, especially aimed at the occurrence of grades 3 to 4 radiation esophagitis and grades 3 to 4 radiation pneumonitis was also instituted.

Point and exact confidence interval estimates of the toxicity and response rates were computed. All time-to-event distribution functions were estimated using standard Kaplan-Meier (KM) methods for censored data, from which the median and other statistics of interest were calculated.

For the biomarker analysis, the baseline enzyme expression levels (ERCC1 and TS) were dichotomized into high (moderate/strong expression) and low levels. The association between the time-to-event outcomes and enzyme levels was explored using KM curves stratified by each enzyme level and explored using Cox model adjusted for histology type. The proportional hazard assumptions were checked using the time-dependent variable models.

All the statistical tests are traditional two sided at $\alpha = 0.05$. Given the nature of this exploratory study, p values are not adjusted for multiple testing.

RESULTS

Patient Characteristics

Twenty-eight patients were enrolled from May 2006 to March 2009 (Table 1). The median age was 60 years, 64% had stage IIIB NSCLC, 68% were men, 54% were current smokers, and 43% had squamous cell histology. The median FEV1 was 2.26 liters (mean 2.31 liters), and the median V20 was 29%; seven patients (25%) had V20 more than 35%.

TABLE 1. Patient Demographics

Demographic Variable	All Patients	Part II Patients[a]
Number	28	21
Age (yr)		
Median	60	62
Sex		
Female	9 (32%)	7 (33%)
Male	19 (68%)	14 (66%)
Race		
White	20 (71%)	15 (71%)
African American	7 (25%)	5 (24%)
Asian	1 (4%)	1 (5%)
Stage		
IIIA	10 (36%)	9 (43%)
IIIB	18 (64%)	12 (57%)
Performance status		
0	7 (25%)	5 (24%)
1	21 (75%)	16 (76%)
Histology		
Squamous	12 (43%)	9 (43%)
Adenocarcinoma	15 (54%)	11 (52%)
Large cell	1 (3%)	1 (5%)
Smoking history		
Never	1 (3%)	1 (5%)
Current	15 (54%)	12 (57%)
Former	12 (43%)	8 (38%)
FEV1		
Median (range)	2.26 liter (1.07–3.43)	2.19 liter (1.07–3.43)
DLCO		
Median (range)	67% (50–100%)	63% (50–92%)
V20		
Median (range)	29% (7–39.6%)	30.6% (7–39.6%)

[a] Patients who received consolidation docetaxel after concurrent therapy.

FEV1, forced expiratory volume in 1 second; DLCO, pulmonary diffusion capacity; V20, total lung volume receiving 20 Gy.

Treatment Delivery

Of the 28 patients who started on therapy, 24 patients (86%) completed all three cycles of cisplatin/pemetrexed. Among the five patients who started cisplatin at 60 mg/m^2, all completed the planned three cycles. Among the 23 patients who started cisplatin at 75 mg/m^2, 19 (83%) completed all three cycles of therapy at full dose and on schedule. Reasons for not completing all cycles of therapy were death (one), progressive disease (one), and toxicities (two; esophagitis and fatigue). Twenty-seven patients completed CRT and received the total planned dose. Five (19%) patients had delays in the radiation therapy, two due to esophagitis, one due to hemoptysis resulting in hospital admission, one due to dehydration, and one due to noncompliance.

Of the 24 patients (three progressed and one died before docetaxel) eligible for docetaxel therapy, 21 patients (88%) went on to receive docetaxel, and 18 patients (86%) completed all three cycles of docetaxel therapy and did so at full dose. Decline in performance status was the reason for three patients not receiving docetaxel. Sixteen patients (57%) completed all components of therapy.

Toxicity

Two patients died while on therapy or soon after. One patient died of severe hematemesis of unclear etiology 1 month after completing concurrent therapy but before the patient could get docetaxel, and the other patient developed a cerebrovascular accident after the first cycle of therapy. Both deaths were considered not to be related to the study treatment. During concurrent therapy, grades 3 to 4 neutropenia occurred in 11 patients (39%), and four patients (14%) developed febrile neutropenia (Table 2). Grade 3/4 esophagitis was observed in four (14%) patients and pneumonitis in one (4%) patient. During concurrent therapy, three patients developed grade 3 renal failure; two patients developed renal failure when admitted for infections and received antibiotics that can be nephrotoxic. All patients recovered their renal function to baseline. Grade $\leq$2 fatigue was a common adverse event observed in 20 patients during concurrent therapy and among 14 patients during docetaxel therapy. Fourteen patients developed symptoms of grade $\leq$2 esophagitis during docetaxel. During concurrent therapy and docetaxel therapy, grade 1 diarrhea

TABLE 2. Grade 3/4 Toxicities During Concurrent Therapy (Part I) and during Docetaxel Therapy (Part II)

	Part I, *N* = 28 (%)	Part II, *N* = 21 (%)
Hematologic toxicities		
WBC	12 (43)	0
Neutrophils	11 (39)	0
Febrile neutropenia	4 (14)	0
Nonhematologic toxicities		
Esophagitis	4 (14)	0
Pneumonitis	1 (4)	0
Hemoglobin	3 (11)	0
Vomiting	1 (4)	0
Hyperglycemia	3 (11)	5 (25)
Hypoglycemia	0	1 (5)
Infection	0	1 (5)
Renal failure	3 (11)	0
Hyponatremia	1 (4)	0
Hyperkalemia	1 (4)	0
Other[a]	0	1 (5)

[a] Patient developed grade 3 hemoptysis.
WBC, white blood cell.

TABLE 3. Survival Outcome: Progression-Free Survival (PFS) and Overall Survival (OS)

	N	Events	Point Estimate	95% Confidence Interval	
PFS	28	20			
Median			16.4 mo	6.7 mo	35.7 mo
1 yr rate			55%	37%	74%
By histology					
Squamous[a]	12	8			
Median			18.7 mo	2.3 mo	45.9 mo
1 yr rate			57%	29%	85%
Nonsquamous[a]	16	12			
Median			13.2 mo	4.2 mo	34.6 mo
1 yr rate			52%	27%	76%
OS	28	14			
Median			33.8 mo	8.0 mo	[b]
1 yr rate			66%	48%	84%
By histology					
Squamous[a]	12	6			
Median			25.2 mo	0.0 mo	[b]
1 yr rate			66%	38%	94%
Nonsquamous[a]	16	8			
Median			35.9 mo	9.3 mo	[b]
1 yr rate			64%	41%	88%

[a] The differences in either PFS or OS between squamous cell patients and patients with nonsquamous histologies were not statistically significant.
[b] These values cannot be calculated (either due to the censoring pattern or else the value is not reached).

occurred in six and two patients, respectively; grade 2 stomatitis occurred in one patient each; and grade 1 neuropathy occurred in one patient each. Late toxicities attributable to the therapy have not been observed to date.

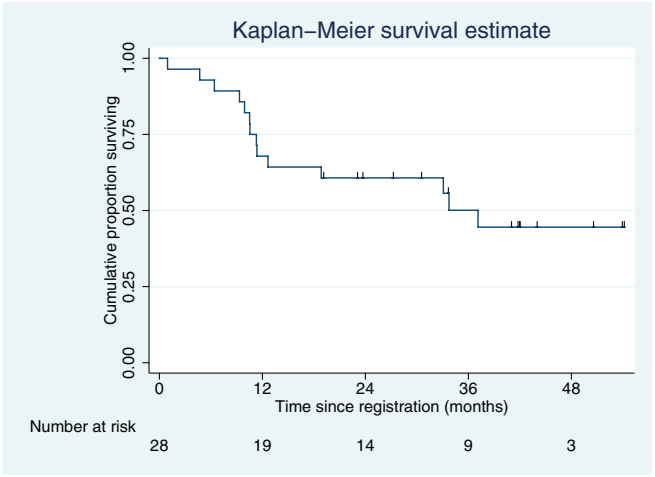

FIGURE 1. Overall survival of all enrolled patients.

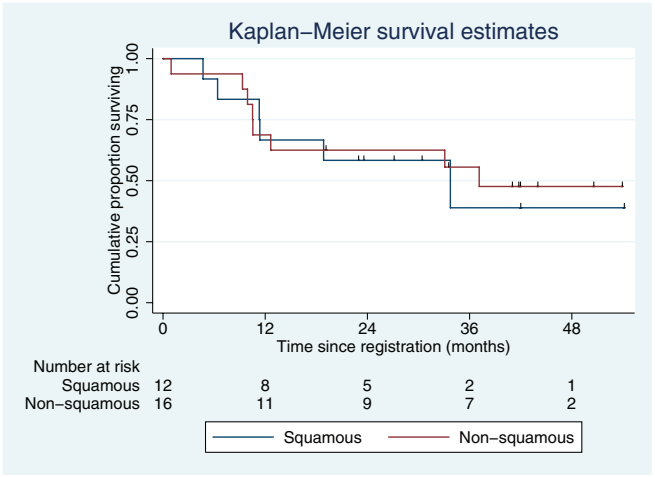

FIGURE 2. Survival of squamous cell patients and nonsquamous cell patients.

Efficacy

The median follow-up for all patients is 41 months (Table 3). The median overall survival (OS) was 34 months and 1-year survival rate was 66% using KM estimate (Figure 1). The median PFS was 16 months, and 1-year PFS rate was 55%. The response rate was 64%. As pemetrexed may not be efficacious in patients with squamous cell carcinoma, we analyzed the outcomes separately in these patients (Figure 2). The median follow-up for squamous cell patients is 29 months, and the median follow-up for nonsquamous patients cell is 41 months. The median PFS in squamous cellpatients and nonsquamous patients were 19 and 13 months, respectively, and the 1-year PFS rate was 57% and 52%, respectively. The median survival of squamous cell patients was 25 months and 36 months in nonsquamous patients. We analyzed the correlation of the following factors: age, sex, histology, smoking status, FEV1 and pulmonary diffusion capacity to survival, and PFS and found none to be significantly associated with OS or PFS (data not shown).

TABLE 4. Expression of ERCC1 and Thymidylate Synthase

Biomarker	Histology		Total ($N = 16$)
	Squamous ($N = 7$)	Adenocarcinoma ($N = 9$)	
ERCC1			
No expression	1	4	5
Weak expression	2	3	5
Moderate expression	3	2	5
Strong expression	1	0	1
TS			
No expression	1	3	4
Weak expression	2	3	5
Moderate expression	1	3	4
Strong expression	3	0	3

TABLE 5. Hazard Ratio (Adjusted for Histology) for Moderate or Strong Expression of ERCC1 and TS

Biomarker	Hazard Ratio	95% CI	*p*
Survival			
ERCC1	2.25	0.47–10.76	0.311
TS	16.65	2.06–134.94	0.0084
PFS			
ERCC1	1.56	0.41–5.89	0.513
TS	8.87	1.76–44.64	0.0081

Patient numbers, 16; moderate or Strong Expression ERCC, 1 to 6/16; moderate or Strong TS, 7/16.

CI, confidence interval; ERCC1, Excision Repair Cross Complementation Group 1; TS, thymidylate synthase; PFS, progression-free survival.

Sites of First Failure

Eighteen patients have developed progression. Four patients (22%) developed brain metastases only as the first site of progression. Five patients (28%) developed distant metastases, other than brain metastases, as the first site of progression, and five patients (28%) developed local progression as the first site of progression. Four patients developed both local and distant progression.

Tumor ERCC1 and TS Expression

The decision to analyze these markers was taken after the study started (Tables 4 and 5). Therefore, only 18 patients could be consented for this assessment, and of these 18 patients, adequate tumor for analysis was available in only 16 patients (nine adenocarcinomas and seven squamous cell carcinomas). The hazard ratios for both survival and PFS were higher for moderate or strong ERCC1 and TS expression, but only the TS expression was significantly associated with both PFS and OS.

DISCUSSION

This is among the first trials to evaluate the combination of cisplatin and pemetrexed administered concurrently with CRT in patients with stage III NSCLC. These results show that it is feasible to combine pemetrexed and cisplatin at full doses with 66 Gy CRT. The 1-year survival of 66% is similar to other regimens, and the median survival of 34 months is very promising.

Despite the acceptance of concurrent therapy as the standard treatment for patients with stage III NSCLC, there is no consensus on the specific chemotherapy regimen. In the United States, the two commonly used regimens are cisplatin/etoposide and weekly carboplatin with paclitaxel. The median survival in phase III trials, with the current regimens, is $\leq$21 months.[5] Based on the results of a phase I trial conducted by Seiwert et al.[6,11] and the results of S9504, we planned the current trial of cisplatin and pemetrexed with CRT followed by three cycles of docetaxel. This treatment plan, therefore, included three of the most active agents for the treatment of NSCLC, with different putative mechanisms of action, providing the possibility of improved local and distant control.

Before the start of this trial, there were no data available regarding the feasibility of combining cisplatin with pemetrexed and CRT. We, therefore, treated the first five patients with a dose of 60 mg/m^2/cycle of cisplatin (total dose, 180 mg/m^2), a dose comparable with the total cisplatin dose of 200 mg/m^2 used in S9504. As these five patients tolerated the concurrent therapy well, we decided to escalate the cisplatin dose to 75 mg/m^2/cycle because this is the dose used when cisplatin is combined with pemetrexed in advanced NSCLC and malignant mesothelioma.[9,15]

The treatment delivery rates in this trial are similar to S9504. Twenty-four (86%) patients completed all three cycles of cisplatin/pemetrexed when compared with 88% of the patients in S9504 completing cisplatin/etoposide. Twenty-one patients (75%) went on to receive docetaxel in this trial and 78% in S9504. The febrile neutropenia rate of 14% in this trial is slightly higher than other concurrent therapy regimens.[6,8,16] Nevertheless, the rate of severe neutropenia at 39% was not excessive. The rates of grade 3/4 esophagitis and pneumonitis, two major adverse events observed with concurrent therapy in patients with NSCLC, were comparable with the rates observed in other trials.

The Cancer and Leukemia Group B (CALGB) recently presented the results of CALGB 30407, a study evaluating the combination of carboplatin area under the curve 5, pemetrexed 500 mg/m^2, and CRT 70 Gy.[17] Patients were also randomized to receive cetuximab or not. After completion of concurrent therapy, patients were to receive four additional cycles of pemetrexed. Of the 99 eligible patients, 85% of the patients completed concurrent therapy. The median survival was 22 months. The incidence of severe neutropenia (50%), febrile neutropenia (7%), esophagitis (28%), and pneumonitis (10%) in the CALGB 30407 trial were similar to the rates observed in the current trial.

Other studies have evaluated the integration of pemetrexed in concurrent treatment strategies for locally advanced NSCLC and found the strategy to be feasible. Brade et al.[18] recently reported results of 39 patients enrolled on a phase II study evaluating the combination of pemetrexed at 500 mg/m^2 on day 1 and cisplatin 20 mg/m^2 on days 1 to 5 every 21 days for two cycles with radiation therapy of 61 to 66 Gy over 6 to 6.5 weeks. After completion of concurrent

therapy, patients were scheduled to receive two more cycles of pemetrexed and cisplatin (75 mg/m^2) every 21 days. Seventy-four percent of patients (29/39) completed all planned four cycles of chemotherapy, which is a higher rate than the rate of 57% observed in this study. The major hematologic toxicity was neutropenia (10 patients), and nonhematologic toxicites were nausea/emesis (n = 4), fatigue/syncope (n = 4),and esophagitis (n = 2). Grade 3/4 pneumonitis was observed in only one patient. The 1-year OS and PFS rates were 80% and 47%, respectively. Similarly, Choy et al.[19] reported the results of an ongoing study randomizing patients with stage III NSCLC to pemetrexed with carboplatin (area under the curve 5) or pemetrexed with cisplatin (75 mg/m^2) administered every 3 weeks for three cycles with radiation therapy of 64 to 68 Gy. Among 71 patients, the combination was well tolerated. The response rates in the carboplatin (15 patients evaluable) and cisplatin (20 patients evaluable) arms were 47% and 60%, respectively. Ma et al. presented their results on 21 patients who underwent two cycles of carboplatin and pemetrexed with 62 Gy radiation therapy followed by three more cycles of carboplatin and pemetrexed. They reported an impressive response rate of 86% and found that the outcomes in patients with adenocarcinoma were better.[20] Mornex et al.[21] recently reported on a phase I study evaluating the strategy of induction therapy with two cycles of pemetrexed and cisplatin followed by pemetrexed with cisplatin and radiation therapy. The investigators found this strategy to be feasible. The main toxicities were cytopenias and nausea and emesis. One patient did develop septic shock. The results from these studies suggest that integration of pemetrexed/platinum combination with radiation therapy for the treatment of stage III NSCLC is feasible. The data regarding toxicity and efficacy in this study are similar to the results reported by other investigators.

The median survival in many phase II trials for stage III NSCLC is in the range of 25 months.[16,22,23] The results of the current trial may be influenced by the stringent eligibility criteria of the study. All the patients in the current trial underwent PET scans, something that was not done routinely in the previous phase II and phase III trials. PET scans permit selection of patients likely to have better outcomes.[24–26] In addition, the eligibility criteria mandated that the V20 should be ≤40%. Previous studies have shown that V20 values can correlate with radiotherapy-related toxicities.[27,28] Southwest Oncology Group presented data showing that patients with V20 more than 35% have inferior survival.[29] Thus, these eligibility criteria, not routinely included in prior studies, may have selected for patients that were likely to have a better outcome.

The benefit of consolidation docetaxel in the current regimen is unclear. We included docetaxel in this regimen because it was the accepted standard at the time this study was initiated. Hoosier Oncology Group LUN 01-24/USO-023 was designed to test the utility of consolidation docetaxel.[30] Growth factors after docetaxel were not mandated, and the eligibility criteria regarding PFTs were less stringent in the HOG trial. The results of this study showed that consolidation docetaxel did not improve survival and increased toxicities. Consolidation docetaxel was well tolerated in the current trial and was not associated with severe toxicities or mortality. It is unclear, if consolidation docetaxel administered with growth factors in patients with adequate PFTs could provide survival advantage. Nevertheless, extending chemotherapy beyond concurrent therapy can be challenging as suggested by less than 60% of the patients completing all planned therapy in the current trial and in CALGB30407.[17] Therefore, the need for docetaxel in this regimen is unclear.

During the trial, it became known that histology is an important predictor of pemetrexed efficacy.[9,10] In this study, there was no difference in efficacy of the regimen based on histologic categories; however, the number of patients were small to be certain of differential efficacy of this regimen in different histologic subtypes. In CALGB30407 as well, there was no significant difference in efficacy between squamous and other histologies. Nevertheless, Ma et al.[20] reported that they found better outcomes in patients with adenocarcinoma with the combination of carboplatin/pemetrexed with radiation therapy. Whether concurrent therapy regimens that include pemetrexed will have differential effects according to histology, as observed in advanced stage NSCLC, will only be clear once the results of all the studies evaluating this strategy are available.

It has been suggested that the lack of efficacy of pemetrexed in squamous cell patients is related to higher TS expression.[31] We analyzed TS and also ERCC1, a possible marker of efficacy for platinum compounds,[32] by immunohistochemistry and found a trend for increased hazard ratio for survival and PFS in patients with tumors that had moderate/strong expression of TS and ERCC1. The hazard ratios for ERCC1 were lower than the hazard ratios for TS, and the association of TS with both survival and PFS was statistically significant. The results of TS and ERCC1 expression in the current trial have to be considered hypothesis generating as the analysis was unplanned and conducted only in 16 patients. The observation that TS expression may have greater association with clinical outcomes in patients treated with this regimen than ERCC1 needs to be assessed in future studies.

The major limitation of this study is the small number of patients. Also the enrollment is only from two sites. When the study was planned, there were no data of combining cisplatin with pemetrexed with radiation therapy, and the amount of data on the use of pemetrexed in patients with NSCLC was limited. We, therefore, designed the study to ensure that the outcome with this regimen was not inferior to the outcomes observed with existing regimens in this potentially curable patient population. The statistical design required enrollment of 28 patients to assess this objective.

In conclusion, the current trial has shown that cisplatin/pemetrexed at full dose with CRT in patients with stage III NSCLC is feasible, and the outcomes of these patients are comparable with current regimens. These results need to be confirmed in larger trials. Currently, there is a phase III trial evaluating the combination of pemetrexed with cisplatin and CRT in patients with nonsquamous NSCLC.[33] The results of this phase III trial will further define the value of integrating

pemetrexed in concurrent therapy for patients with stage III NSCLC.

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