Overview

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Title: *nab*-Paclitaxel in Combination With Weekly Carboplatin With Concurrent Radiotherapy in Stage III Non-Small Cell Lung Cancer

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

Unresectable stage III non-small cell lung cancer (NSCLC) has a 5-year survival rate of 20%, and concurrent chemoradiotherapy results in significant toxicity with the use of current chemotherapeutic agents. *nab*-Paclitaxel was approved by the U.S. Food and Drug Administration in October 2012 for use along with carboplatin in advanced NSCLC. This study was undertaken to determine the maximum tolerated dose and dose-limiting toxicities (DLTs) of weekly *nab*-paclitaxel given in combination with carboplatin and concurrent radiotherapy in patients with unresectable stage III NSCLC.

Methods

Escalating doses of once-weekly *nab*-paclitaxel were given along with once-weekly carboplatin area under the plasma concentration time curve (AUC) of 2 and concurrent radiotherapy 66 Gy in 33 fractions, followed by 2 cycles of carboplatin and *nab*-paclitaxel consolidation chemotherapy.

Results

Eleven patients were enrolled and received treatment per protocol, with 10 evaluable for efficacy and toxicity. At dose level 1 (*nab*-paclitaxel 60 mg/m^2), 2 DLTs were observed: esophagitis and radiation dermatitis. Six patients were enrolled at dose level 0 (*nab*-paclitaxel 40 mg/m^2) with no DLTs. Nine of 10 evaluable patients had a partial response.

Conclusion

Concurrent chemoradiotherapy with *nab*-paclitaxel 40 mg/m^2 and carboplatin AUC 2 is a safe and well-tolerated therapeutic regimen in patients with stage III NSCLC. A separate phase I/II study to evaluate the efficacy of this regimen is under way.

Discussion

In this phase I trial with 10 evaluable patients with stage III NSCLC, the concomitant use of weekly *nab*-paclitaxel and carboplatin with concurrent radiotherapy was demonstrated to be a safe therapeutic approach. The maximum tolerated dose was *nab*-paclitaxel 40 mg/m^2 with carboplatin AUC 2 along with daily radiotherapy to a dose of 66 Gy in 33 fractions. There was no DLT at this dose level. Adverse events (AEs) were common but expected, given this modality of therapy and stage of disease. In fact, the range and grade of AEs were similar to previous trials using concurrent chemoradiotherapy for stage III disease [1, 2].

Because of the nature of a phase I trial and the small number of patients enrolled, it is not appropriate to draw meaningful conclusions concerning overall response rate (ORR) or survival. In this trial, however, 30% of the patients were alive ~3 years after enrollment, a result similar to the acknowledged survival pattern for patients with stage III NSCLC [1, 2]. In addition, the ORR in this small phase I trial was 90%, with 9 patients experiencing a partial response by RECIST. Phase III trials of combination chemoradiotherapy in stage III disease have reported ORRs between 50% and 80% [5–7].

There is significant room for improvement in the treatment of stage III NSCLC. To that end, numerous cytotoxic agents and novel therapies have been tested or are being evaluated in this cohort of patients. Its effectiveness in this population will require further investigation, and a phase I/II trial is ongoing comparing radiotherapy given concurrently with either carboplatin plus *nab*-paclitaxel or carboplatin plus paclitaxel (ClinicalTrials.gov identifier NCT00544648).

Trial Information

Disease	Lung cancer – NSCLC
Stage of disease / treatment	Primary
Prior Therapy	None
Type of study - 1	Phase I
Type of study - 2	Other
Primary Endpoint	Maximum Tolerated Dose
Secondary Endpoint	Safety
Investigator's Analysis	Drug Tolerable, Efficacy Indeterminate

Drug Information

Drug 1 **Generic/Working name**	*nab*-Paclitaxel
Trade name	Abraxane
Company name	Celgene
Drug type	Other
Drug class	Microtubule-targeting agent
Dose	milligrams (mg) per square meter (m^2)
Route	IV
Schedule of Administration	Intravenously weekly along with weekly carboplatin AUC 2 and concurrent daily radiotherapy. Patients without evidence of progression following radiotherapy were then treated with consolidation chemotherapy consisting of two cycles of *nab*-paclitaxel 100 mg/m^2 administered weekly (days 1, 8, 15) along with carboplatin AUC 6 administered on day 1 of each 21-day cycle.

Drug 2 **Generic/Working name**	Carboplatin
Trade name	Paraplatin
Drug type	Other
Drug class	Platinum compound
Dose	AUC 2 during concurrent chemoradiation phase and AUC 6 during consolidation chemotherapy phase
Route	IV
Schedule of Administration	Intravenously weekly along with *nab*-paclitaxel and concurrent daily radiotherapy. Patients without evidence of disease following radiotherapy were then treated with consolidation chemotherapy consisting of two cycles of *nab*-paclitaxel 100 mg/m^2 administered weekly (days 1, 8, 15) along with carboplatin AUC 6 administered on day 1 of each 21-day cycle.

Dose Escalation Table

Dose Level	Dose of Drug: nab-paclitaxel	Dose of Drug: Carboplatin	Number Enrolled	Number Evaluable for Toxicity
0	40 mg/m^2 weekly	AUC 2	6	6
1	60 mg/m^2 weekly	AUC 2	4	4

Patient Characteristics

Number of patients, male	9
Number of patients, female	2
Stage	IIIA – 7IIIB – 4
Age	Median (range): 63 (45-75)
Number of prior systemic therapies	Median (range): 0
Performance Status:	ECOG • 0 — 7 • 1 — 4 • 2 — 0 • 3 — 0 • unknown — 0
Other	Pulmonary Function Tests (FEV1): Median 2.07 (L) Range 1.02-3.34 (L)
Cancer Types or Histologic Subtypes	• Adenocarcinoma 6 • Squamous Cell Carcinoma 3 • NSCLC NOS 1 • Large Cell Carcinoma 1

Primary Assessment Method

Control Arm: Total Patient Population

Number of patients enrolled	11
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10
Evaluation method	RECIST 1.0
Response assessment CR	0
Response assessment PR	90
Response assessment SD	10
Response assessment PD	0
Response assessment OTHER	0

(Median) duration assessments PFS	7.7 months, CI: 95% (6.5-∞)
(ξ) (Median) duration assessments OS	19.2 months, CI: 95% (11.0-∞)

Adverse Events During Concurrent Chemoradiation Phase

Adverse Events At All Dose Levels, All Cycles

Name	*NC/NA	1/2	3/4	5	All Grades
Neutrophils/granulocytes (ANC/AGC)	70%	20%	10%	0%	30%
Platelets	70%	30%	0%	0%	30%
Fatigue (asthenia, lethargy, malaise)	50%	50%	0%	0%	50%
Rash: dermatitis associated with radiation	80%	10%	10%	0%	20%
Esophagitis	80%	20%	0%	0%	20%
Nausea	70%	30%	0%	0%	30%
Glucose, serum-high (hyperglycemia)	70%	30%	0%	0%	30%
Pain	70%	30%	0%	0%	30%
Cough	50%	50%	0%	0%	50%
Dyspnea (shortness of breath)	60%	40%	0%	0%	40%
Thrombosis/thrombus/embolism	90%	0%	10%	0%	10%
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC $<1.0 \times 10^9$/L, fever $\geq$38.5°C)	90%	0%	10%	0%	10%

Adverse Events Legend
*No Change from Baseline/No Adverse Event
Select NCI toxicities listed by number of patients.

Adverse Events During the Consolidation Chemotherapy Phase

Adverse Events At All Dose Levels, All Cycles

Name	*NC/NA	1/2	3/4	5	All Grades
Hemoglobin	40%	50%	10%	0%	60%
Neutrophils/granulocytes (ANC/AGC)	70%	0%	30%	0%	30%
Platelets	70%	0%	30%	0%	30%
Fatigue (asthenia, lethargy, malaise)	60%	40%	0%	0%	40%
Nausea	90%	10%	0%	0%	10%
Glucose, serum-high (hyperglycemia)	60%	40%	0%	0%	40%
Cough	90%	10%	0%	0%	10%
Dyspnea (shortness of breath)	90%	10%	0%	0%	10%
Thrombosis/thrombus/embolism	90%	0%	10%	0%	10%
Rash: dermatitis associated with radiation	80%	20%	0%	0%	20%
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC $<1.0 \times 10^9$/L, fever $\geq$38.5°C)	90%	0%	10%	0%	10%
Sodium, serum-low (hyponatremia)	80%	10%	10%	0%	20%

Adverse Events Legend
*No Change from Baseline/No Adverse Event
Select NCI toxicities listed by number of patients.

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not Collected
Investigator's Assessment	Drug Tolerable, Efficacy Indeterminate

Discussion

In this phase I trial of 10 evaluable patients with stage III non-small cell lung cancer (NSCLC), the concomitant use of weekly *nab*-paclitaxel and carboplatin with concurrent radiotherapy was demonstrated to be a safe therapeutic approach. The maximum tolerated dose was *nab*-paclitaxel 40 mg/m^2 with carboplatin area under the plasma concentration time curve of 2 along with daily radiotherapy to a dose of 66 Gy in 33 fractions. There was no dose-limiting toxicity at this dose level. Adverse events (AEs) were common, but expected given this modality of therapy and stage of disease. In fact, the range and grade of AEs were similar to previous trials using concurrent chemoradiotherapy for stage III disease [1, 2]. Interestingly, despite the lack of systemic glucocorticoids, there were no reported infusion reactions or cases of peripheral neuropathy in this trial, both of which are known to occur with the use of paclitaxel [3, 4].

Because of the nature of a phase I trial and the small number of patients enrolled, it is not appropriate to draw meaningful conclusions concerning overall response rate (ORR) or survival. In this trial, however, 30% of the 10 evaluable patients were alive ~3 years after enrollment, a result similar to the acknowledged survival pattern for patients with stage III NSCLC [1, 2]. In addition, the ORR in this small phase I trial was 90%, with the 9 patients experiencing a partial response by RECIST. Phase III trials of combination chemoradiotherapy in stage III disease have reported ORRs between 50% and 80% [5–7].

There is significant room for improvement in the treatment of stage III NSCLC. To that end, numerous cytotoxic agents and novel therapies have been tested or are being evaluated in this cohort of patients. Cetuximab, bevacizumab, erlotinib, and a host of other biological agents are being tested but have not yet replaced the standard of care of concurrent platinum chemotherapy [8–12]. If proven effective and safe in further clinical trials, *nab*-paclitaxel could be an attractive option for patients treated with concurrent chemoradiotherapy because it is approved by the U.S. Food and Drug Administration for use in metastatic lung cancer. In addition, it may lessen side effects that are often caused by paclitaxel such as peripheral neuropathy and infusion reactions.

Effectiveness in this population will require further investigation, and a phase I/II trial is ongoing comparing radiotherapy given concurrently with either carboplatin plus *nab*-paclitaxel or with carboplatin plus paclitaxel (ClinicalTrials.gov identifier NCT01757288).

References

1. Dillman RO, Herndon J, Seagren SL et al. Improved survival in stage III non-small-cell lung cancer: Seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. J Natl Cancer Inst 1996;88:1210–1215.
2. Okawara G, Mackay JA, Evans WK et al. Management of unresected stage III non-small cell lung cancer: A systematic review. J Thorac Oncol 2006;1:377–393.
3. Tsavaris NB, Kosmas C. Risk of severe acute hypersensitivity reactions after rapid paclitaxel infusion of less than 1-h duration. Cancer Chemother Pharmacol 1998;42:509–511.
4. Weiss RB, Donehower RC, Wiernik PH et al. Hypersensitivity reactions from Taxol. J Clin Oncol 1990;8:1263–1268.
5. Jain AK, Hughes RS, Sandler AB et al. A phase II study of concurrent chemoradiation with weekly docetaxel, carboplatin, and radiation therapy followed by consolidation chemotherapy with docetaxel and carboplatin for locally advanced inoperable non-small cell lung cancer (NSCLC). J Thorac Oncol 2009;4:722–727.
6. Choy H, Devore RF III, Hande KR et al. A phase II study of paclitaxel, carboplatin, and hyperfractionated radiation therapy for locally advanced inoperable non-small-cell lung cancer (a Vanderbilt Cancer Center Affiliate Network Study). Int J Radiat Oncol Biol Phys 2000;47:931–937.
7. Ratanatharathorn V, Lorvidhaya V, Maoleekoonpairoj S et al. Phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small-cell lung cancer. Lung Cancer 2001;31:257–265.
8. Govindan R, Bogart J, Stinchcombe T et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol 2011;29:3120–3125.
9. Blumenschein GR Jr., Paulus R, Curran WJ et al. Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. J Clin Oncol 2011;29:2312–2318.
10. Socinski MA, Stinchcombe TE, Moore DT et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: Results of a phase I/II trial. J Clin Oncol 2012;30:3953–3959.
11. Lind JS, Senan S, Smit EF. Pulmonary toxicity after bevacizumab and concurrent thoracic radiotherapy observed in a phase I study for inoperable stage III non-small-cell lung cancer. J Clin Oncol 2012;30:e104–e108.
12. Stinchcombe TE, Bogart JA. Novel approaches of chemoradiotherapy in unresectable stage IIIA and stage IIIB non-small cell lung cancer. ***The Oncologist*** 2012;17:682–693.

Tables

Table 1. Prespecified dose levels

Dose level	Radiation (Gy/fraction)	Carboplatin (AUC)	*nab*-Paclitaxel (mg/m^2)
−2	2	2	20
−1	2	2	30
0	2	2	4
1	2	2	60
2	2	2	80
3	2	2	100

Abbreviation: AUC, area under the plasma concentration time curve.

Table 2. Individual patient outcomes

Patient	Dose level	Histology	Radiation	Response	DLT	OS (days)
1-01	0	ADC	3D	SD	None	372
1-02	0	SCC	3D	PR	None	1,427[a]
1-03	0	NSCLC NOS	3D	PR	None	1,273[a]
2-04	1	LCC	3D	PR	Esophagitis	601
2-05	1	ADC	3D	PR	None	1,289[a]
2-06	1	SCC	3D	PR	None	766[a]
2-07	1	ADC	3D	PR	Radiation dermatitis	325
1-08	0	ADC	3D	PR	None	330
1-09	0	SCC	IMRT	PR	None	551
1-10	0	ADC	IMRT	PR	None	258

[a]Patient was alive at last visit.
Abbreviations: 3D, three-dimensional conformal radiation; ADC, adenocarcinoma; DLT, dose-limiting toxicity; IMRT, intensity-modulated radiation therapy; LCC, large cell carcinoma; NSCLC NOS, non-small cell lung cancer, not otherwise specified; OS, overall survival; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.