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A phase II trial of high dose carboplatin and paclitaxel with G-CSF and peripheral blood stem cell support followed by surgery and/or chest radiation in patients with stage III non-small cell lung cancer: CALGB 9531

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Abstract

Purpose—We designed a phase II trial to evaluate the efficacy and tolerability of high dose induction chemotherapy with carboplatin and paclitaxel with G-CSF and stem cell support followed by surgical resection and/or chest radiotherapy in patients with stage III non-small cell lung cancer (NSCLC).

Patients and methods—Patients had pathologically confirmed stage IIIA–IIIB NSCLC, adequate end-organ function, no prior chemotherapy or radiation, and performance status 0–1. Peripheral stem cells were mobilized with G-CSF stimulation on days 1–5 and collected prior to chemotherapy. Chemotherapy consisted of 2 cycles of paclitaxel 250 mg/m² over 3 h and carboplatin at an AUC 18 on days 11 and 32, each followed by stem cell reinfusion. Stable and responding patients went on to surgical resection (in patients deemed resectable) followed by post-operative radiation, or to conventional chest radiotherapy to 66 Gy in unresectable patients.

Results—Twelve patients (11 eligible) were accrued from 1996 to 1999. The 11 patients were predominately male (64%), white (82%), of performance status 0 (64%), and with weight loss less than 5% (55%). The median age was 51 (range 31–63). Ten (10) patients (91%) experienced grade 4 toxicity. There were no lethal toxicities. Grade 3–4 toxicities most commonly reported included: platelets (100%), lymphocytopenia (91%), leukopenia (91%), neutropenia (73%), anemia (55%), pain (45%), and nausea (27%). Three patients (27%) had a partial response to induction chemotherapy. Of the 11 patients, 7 underwent surgical exploration, and 10 received radiation. Two patients were completely resected, 3 patients had incomplete resections, and 2 patients had no resection. There were 4 complete responses and 3 partial responses following surgery and/or radiation. The median overall survival time was 17.8 months. The median failure-free survival time was 8.3 months. One-year and 2-year overall survival are estimated at 64% and 27%, respectively.

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Conflict of interest statement

Drs. Masters, Vokes, and Green and Mr. Wang and Ms. Hodgson disclose no potential conflicts of interest.

Conclusions—High dose induction chemotherapy with carboplatin and paclitaxel and stem cell support in patients with stage IIIA–IIIB NSCLC produced response rates and survival similar to standard therapy. Excessive toxicity (and cost) suggests that this approach does not merit further investigation.

Keywords

Non-small cell lung cancer; Chemotherapy; Radiotherapy; Surgery; Carboplatin; Paclitaxel; High dose chemotherapy; Stem cell transplant

1. Introduction

Non-small cell lung cancer (NSCLC) is the most common cause of cancer death in the U.S. [1]. Approximately 20–30% of patients present with locally advanced, stage III disease. Prognosis is guarded, but these patients are potentially curable [2]. However, the optimal management remains controversial. Treatment modalities including surgery, radiation, and chemotherapy must be integrated for effective multi-disciplinary care. The optimal regimen, dose, schedule, and timing of chemotherapy for incorporation into multimodality programs have yet to be determined. Stage IIIA patients treated with surgery alone have a poor outcome with over 80% recurring locally, in regional lymphatics, or at distant sites [3]. Postoperative radiation therapy can improve local control, but still results in few long-term survivors for stage IIIA NSCLC [4]. Unresectable stage IIIA–IIIB tumors are generally treated with chemotherapy and radiation. While symptoms are improved, systemic progression outside the radiated field is frequent.

A combined modality approach incorporating radiation, chemotherapy, and surgery when possible may offer stage III NSCLC patients the best chance for long-term control of their disease [5]. Several randomized trials have proven the benefit of chemotherapy given prior to radiation (RT) in locally advanced NSCLC. The CALGB reported an improved outcome with 2 cycles of cisplatin–vinblastine prior to RT with a median survival of 14 vs. 10 months and 5-year survival of 19% vs. 7% when compared to RT alone [6]. An intergroup trial conducted through the RTOG confirmed the benefit of this combined approach in unresectable stage III patients [7].

Similarly, induction chemotherapy has also proven beneficial in resectable stage III patients, with 2 randomized trials showing a survival benefit for induction chemotherapy and surgery over surgery alone [8, 9]. The role of surgical resection in this population is also unclear. Preliminary results of a randomized study that compared chemoradiotherapy to induction chemoradiotherapy followed by surgery showed no survival advantage in the surgical arm, although a significant prolongation in disease-free survival was seen [10].

Thus, the addition of chemotherapy has resulted in improved outcome for both surgical and unresectable stage III NSCLC patients. Still, more than 75% of patients relapse and die of metastatic cancer. The identification of new strategies to improve survival in locally advanced non-small cell lung cancer remains a high priority.

High dose chemotherapy (HDC) in the management of solid tumors gained popularity after early phase I and II studies suggested an improvement in outcome for advanced breast and small cell lung cancers, based on the theory that there is a dose–response relationship with chemotherapy drugs [11–13]. While more recent randomized trials suggest this may have been due to patient selection rather than more effective tumor control [14], we hypothesized at the time this study was designed that locally advanced NSCLC patients might benefit from a more intensive induction chemotherapy regimen to help eradicate micrometastatic disease, with standard local therapy to control bulk disease in the chest. Early results from a phase I trial at Duke in patients with advanced cancer including metastatic NSCLC showed the feasibility of high dose chemotherapy with paclitaxel and carboplatin and stem cell support. Six of seven NSCLC patients had an objective response to treatment [15]. Myelosuppression was the dose limiting toxicity in this study.

The dose limiting toxicity of carboplatin is myelosuppression [16]. Principal toxicities of paclitaxel administration include neutropenia, thrombocytopenia, anemia, allergic infusion reactions and peripheral neuropathy [17]. Phase I studies in combination with carboplatin identified a maximum tolerated dose of paclitaxel of 250 mg/m² [18]. The combination regimen of carboplatin and paclitaxel has shown response rates from 28 to 62% in advanced NSCLC [19, 20]. Therefore, the combination of carboplatin and paclitaxel is one standard chemotherapy regimen for both locally advanced disease and metastatic NSCLC, and carboplatin dose escalation was considered feasible.

At the time of this trial design, there was enthusiasm for high dose chemotherapy to improve outcome in patients with advanced solid tumors. We therefore designed this trial to evaluate the potential efficacy of this technique in locally advanced NSCLC, where systemic recurrence rates are high, but standard chemotherapy had shown the ability to improve survival, presumably by eradicating microscopic metastatic disease. In theory, then, higher doses of chemotherapy might kill a larger fraction of metastatic cells, improving outcome.

2. Patients and methods

2.1. Patient selection

The study was conducted at individual CALGB sites and approved by the local Institutional Review Boards. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines. Eligibility criteria were as follows: (1) stage IIIA or IIIB non-small cell lung cancer (without a malignant pleural effusion) as defined by the AJCC (4th edition) staging system; (2) histologic or cytologic documentation of non-small cell lung cancer; (3) measurable or evaluable disease; (4) performance status 0–1; (5) adequate laboratory parameters indicating appropriate end-organ function, including estimated GFR > 60 ml/min/1.74 m² BSA, ANC > 1500, platelets > 100,000, bilirubin < 1.5 mg/dl, SGOT < 2 × upper limit of normal, and FEV-1 > 11; (6) no prior thoracic radiation or chemotherapy; (7) no active infection or other severe complicating medical illness; (8) age ≥ 18; (9) no concurrent malignancy except cervical CIS or non-melanoma skin cancer. All patients underwent surgical mediastinal lymph node staging.

2.2. Treatment plan

Patients initially had peripheral blood stem cells mobilized with filgrastim (G-CSF) at 10 mcg/kg/day subcutaneously on days 1–5. Stem cells were collected to achieve a minimum total CD-34+ cell count of 2×10^6 cells/kg and 2×10^8 mononuclear cells/kg. The treatment schema is displayed in Fig. 1. Induction chemotherapy consisted of two 21-day cycles of carboplatin and paclitaxel. Carboplatin was be dosed at a target AUC of 18, and was given intravenously over 30 min on days 11 and 32 for two cycles. The actual carboplatin dose was to be calculated using the calculated creatinine clearance [21] based on the Calvert Formula [22]. Paclitaxel was given at 250 mg/m² IV over 3 h on days 11 and 32 (following carboplatin). Antiemetics and other supportive care were provided at the treating physician's discretion. On day 32, chemotherapy was held for up to 2 weeks for myelosuppression (ANC < 1500, platelets < 50,000). One half of the stem cell product was re-infused on day 13 and the second half on day 34 (48 h after completion of chemotherapy). Patients who experienced grade 3 non-hematologic toxicity or grade 4 myelosuppression lasting more than 7 days during cycle one continued therapy on protocol (after recovery to <grade 2 toxicity) with dose reductions of 25% of both carboplatin and paclitaxel.

Chest radiotherapy was delivered in 200 cGy single daily fractions (5 days per week, Monday to Friday) for a planned total of approximately 30–33 fractions or 6 treatment weeks (total radiotherapy course of 60–66 Gy). Fractionation using 180 cGy per day was also permitted. Treatment was delivered with megavoltage equipment with a nominal energy above 6–25 MV. The original treatment volume included the primary lesion and clinically involved lymph nodes with a 2 cm margin. Elective nodal radiation included draining lymph nodes in the ipsilateral hilum and mediastinum to the suprasternal notch, extending down to 4 cm below the carina. A single continuous radiation field was employed. The boost volume was based on restaging post-chemotherapy CT scans to include primary tumor volume and hilar and ipsilateral mediastinal lymph nodes. Treatment technique was individualized for each patient. Computer tomography based treatment planning was used.

Initial treatment was delivered using an AP/PA technique. Oblique field arrangements were necessary to boost the mediastinum and areas with gross disease. These were instituted at the appropriate times to minimize dose to normal lung and keep the dose to the spinal cord under 49 Gy. The timing of field arrangement changes was left to the discretion of the radiation oncologist and was based on the above considerations. The total radiation dose to grossly uninvolved mediastinum, supraclavicular fossae or hilum was 44 Gy. The total radiation dose to areas of gross disease was up to 66 Gy in patients deemed unresectable/inoperable at initial enrollment.

Tumor resectability was determined after completion the two cycles of chemotherapy by the attending thoracic surgeon. T4 or N3 (IIIB) patients were not considered resectable. A complete mediastinal lymph node dissection was recommended for all patients undergoing surgery. Patients undergoing complete resection with negative margins received 50 Gy of post-operative radiation to the bronchial stump, ipsilateral hilum and mediastinum with 2 cm, 1.5 cm, and 1 cm margins, respectively.

2.3. Statistical methods

Our primary objective was to assess response rate to high dose induction chemotherapy with stem cell rescue in patients with stage III NSCLC. Secondary objectives were to define the toxicities of high dose induction chemotherapy with stem cell rescue in patients with stage III NSCLC, to determine the safety and efficacy of this strategy in combination with radiation $\pm$ surgical resection, to estimate the pathologic complete response rate in resected patients, to evaluate patterns of relapse and time to progression, and to assess pharmacokinetics of paclitaxel and carboplatin in this combination (to be reported separately). The study planned to enroll a maximum of 45 eligible patients to differentiate a response rate (complete, partial, and regression) of 40% or lower vs. 60% or higher at a significance level of 0.1 and about 90% power. A two-stage phase II design [23] with 20 patients in the first stage and additional 25 patients in the second stage was proposed. If 6 or fewer of the first 20 patients responded to treatment, the study would close due to lack of efficacy. However, the study was terminated early before reaching its accrual goal for the first stage due to slow accrual and a lack of enthusiasm to continue the trial.

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. Statistical analyses were performed by CALGB statisticians. The analytic results were based on the data available on January 8, 2003. Exact binomial confidence interval was calculated for response rate. The Kaplan–Meier estimator was used to describe overall survival and failure-free survival. Failure was defined as progression, relapse or death, whichever came first. Complete response was defined as disappearance of all measurable or evaluable disease, signs, symptoms, and biochemical changes related to the tumor for at least 4 weeks during which no new lesions may have appeared. Partial response was defined as reduction by at least 50% of the products of the longest perpendicular diameters of the most easily measurable or largest tumor mass (indicator lesion), without growth of other lesions and the appearance of new lesions (this study was performed before RESIST criteria became standard). Stable disease was defined as indicator lesion increases in size by $<25\%$ or decreases by less than 50% with no new lesions, and progression of disease as an increase by $>25\%$ of the product of perpendicular diameters at the indicator lesion or the appearance of new metastatic lesions. Response rate after induction chemotherapy was expressed as the proportion of patients demonstrating a complete and/or partial response based on all evaluable patients treated with two cycles of therapy [24] (Fig. 2).

3. Results

CALGB 9531 was activated April 15, 1996 and closed early July 15, 1999 due to poor accrual. Twelve patients were accrued to CALGB 9531, but one patient was removed from the analysis: this patient was deemed ineligible due to a secondary malignancy and a pleural effusion. The patient received treatment off protocol. Patients were enrolled from four different institutions.

3.1. Patient characteristics

Characteristics of the (11) patients included in the CALGB 9531 analysis, are summarized in Table 1. These 11 patients were predominately male (64%), white (82%), performance status = 0 (64%), with measurable disease (100%), weight loss less than 5% (55%) and with duration of symptoms less than 6 months (72%). The median age was 51 with a range of 31–63.

Follow-up information was available for all 11 patients. Of these 11 patients, all had adequate stem cell harvest for high dose chemotherapy and 9 completed both cycles of chemotherapy, three with dose reduction for toxicity. Seven patients underwent surgery. All seven patients undergoing surgery had a residual mass with viable tumor present. Two patients had complete resections, 3 patients had incomplete resections, and 2 patients were deemed unresectable at the time of surgery. Ten patients received radiation to the prescribed dose of 60–66 Gy.

3.2. Toxicity

Table 2a summarizes the toxicity experienced by patients during chemotherapy (cycles 1 and 2). Table 2b summarizes the toxicity experienced by patients during the radiation. Ten (10) patients (91%) experienced life-threatening grade 3–4 toxicity. There were no lethal toxicities. Those severe or life threatening toxicities most commonly reported included: platelets (100%), lymphocytopenia (91%), leukopenia (91%), granulocytopenia (73%), anemia (55%), pain (45%), and nausea (27%).

3.3. Response and survival results

3.3.1. Response—Table 3a summarizes best response to chemotherapy (cycles 1–2 of the protocol treatment). Three patients (27%) had a partial response. Table 3b summarizes the best responses that the patients experienced to the full protocol therapy, including surgical resection and radiation. There were 4 complete responses and 3 partial responses following all therapy.

3.3.2. Survival—Table 4 contains statistics for overall survival and failure-free survival. The median overall survival time is 17.8 months with a 95% confidence interval of (10.3 months, NE). The median failure-free survival time is 8.3 months with a 95% confidence interval of (7.7 months, NE). Failure was defined as progression, relapse or death. One-year and 2-year overall survival are estimated at 64% and 27%, respectively. Survival estimates are shown in Table 4, but due to the small number of patients with events after 1-year, these estimates are imprecise.

4. Discussion

The treatment of patients with stage III NSCLC continues to frustrate clinicians and patients alike. While chemotherapy has been shown to improve survival in combination with radiation and/or surgery, no optimal treatment regimen has been defined. Various techniques to both maximize local control and reduce systemic spread have produced haltingly slow progress in this battle. Induction chemotherapy was the best strategy at the time this trial was

designed. Since then, concurrent chemotherapy, post-treatment consolidation chemotherapy and integration of appropriately targeted biologic therapies have all been studied. None has yet proven ideal.

This study attempted to employ one of the most promising techniques available in the early 1990s, high dose chemotherapy with stem cell rescue. Dramatic improvements were not observed, but the treatment was administered safely, without treatment related deaths. Nonetheless, the results presented here do not seem to justify the expense or added toxicity of such an approach, especially in light of newer evidence that high dose chemotherapy offers little benefit in other solid tumors [25]. In fact, investigators voted with their feet in the case of this trial and complete accrual goals were not met based on lack of interest from physicians (and patients as well, no doubt). Still, newer areas of interest such as dose dense therapy continue to garner support among some investigators.

Of the four complete responses to therapy, there were no radiologic or pathologic complete responses observed in this trial following high dose induction chemotherapy. In fact, the overall response rate to induction of 27% would not suggest that any dose response relationship at all exists for carboplatin in NSCLC. This suggests that dose intensification is not likely to be an effective strategy with these agents, in NSCLC with bulk disease. Whether there is a role in the post-operative adjuvant setting when residual tumor burden is minimal remains unclear.

Similarly, whether the currently available chemotherapy drugs, in any combination, dosing schedule, or sequence will offer additional benefit to that seen to date in locally advanced NSCLC patients remains unclear. Rather, the integration of newer target-directed therapy, based on genetic and molecular signatures of cancer cells, seems to hold the greatest promise for future progress. In the meantime, we continue to try to offer our patients the most effective agents at our disposal for even a small improvement in systemic disease control. The combination of carboplatin and paclitaxel in standard doses, in conjunction with radiation (and perhaps surgery in selected patients) continues to be an accepted, standard approach in this population 15 years after this study was devised.

Fortunately, lethal toxicity was not observed in this trial, although grade 3–4 toxicities, especially hematologic, were high, with 91% of patients experiencing some grade 4 toxicity. Albain reported a treatment-related death rate of 10% in a SWOG phase II trial of induction chemoradiotherapy with cisplatin and etoposide [26] prior to surgical resection. A similar death rate of 7% was observed in a randomized phase III trial (Albain) involving the same induction regimen. Postoperative morbidity and mortality may be higher with induction chemoradiotherapy as compared to induction chemotherapy [27]. Any advantage of induction chemoradiotherapy compared to induction chemotherapy alone must be balanced with the potentially higher toxicities of combined modality therapy, especially treatment related deaths. A randomized trial of chemotherapy vs. chemoradiotherapy, each followed by surgical resection in stage IIIA NSCLC (RTOG 0241), was closed early due to poor accrual, and future such trials are unlikely to be completed.

In conclusion, we have demonstrated the feasibility of high dose induction therapy with carboplatin and paclitaxel and stem cell support in stage III NSCLC. Failure to identify a clinical benefit, however, will limit its clinical applicability. Future research will need to explore specific molecular targets for more effective and individualized anti-neoplastic therapy.

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Fig. 1.
Treatment schema.

Fig. 2.
CALGB 9531 overall survival and failure free survival.

Table 1

Patient characteristics.

Variable	Number of Patient (%)
Gender:	
Male	7 (64%)
Female	4 (36%)
Age:	
<50	3 (27%)
50–59	7 (64%)
60–69	1 (8%)
Median	51
Range	31, 63
Race:	
White	9 (82%)
Hispanic	1 (9%)
Black	1 (9%)
Performance status:	
0	7 (64%)
1	4 (36%)
Disease assessment:	
Measurable	11 (100%)
Evaluable	0 (0%)
Weight loss:	
<5%	6 (55%)
5–10%	3 (27%)
Unknown	2 (18%)
Symptom duration:	
<3 months	4 (36%)
3–6 months	4 (36%)
>6 months	1 (9%)
Unknown	2 (18%)

Table 2a

Toxicity for patients on chemotherapy (cycles 1–2).

	Grade of toxicity			<i>N</i>
	3 (Sevr)	4 (L.T.)	5 (Leth)	
WBC	7 (64%)	3 (27%)	0 (0%)	11
Platelets	2 (18%)	9 (82%)	0 (0%)	11
Hemoglobin	6 (55%)	0 (0%)	0 (0%)	11
Granulocytes/bands	2 (18%)	6 (55%)	0 (0%)	11
Lymphocytes	2 (18%)	8 (73%)	0 (0%)	11
Hemorrhage	1 (9%)	0 (0%)	0 (0%)	11
Infection	2 (18%)	0 (0%)	0 (0%)	11
Nausea	2 (18%)	1 (9%)	0 (0%)	11
Vomiting	2 (18%)	0 (0%)	0 (0%)	11
Diarrhea	1 (9%)	0 (0%)	0 (0%)	11
Esophagitis/dysphagia	1 (9%)	0 (0%)	0 (0%)	11
Creatinine	1 (9%)	0 (0%)	0 (0%)	11
Pulmonary edema	1 (9%)	0 (0%)	0 (0%)	11
Ards	1 (9%)	0 (0%)	0 (0%)	11
Other pulmonary	2 (18%)	0 (0%)	0 (0%)	11
Dysrhythmias	1 (9%)	0 (0%)	0 (0%)	11
Hypotension	2 (18%)	0 (0%)	0 (0%)	11
Phlebitis/thrombosis	2 (18%)	0 (0%)	0 (0%)	11
Pain	5 (45%)	0 (0%)	0 (0%)	11
Malaise/fatigue	1 (9%)	0 (0%)	0 (0%)	11
Hyperglycemia	1 (9%)	0 (0%)	0 (0%)	11
Maximum toxicity	1 (9%)	10 (91%)	0 (0%)	11

Table 2b

Toxicity for patients on radiation.

	Grade of toxicity			<i>N</i>
	3 (Sevr)	4 (L.T.)	5 (Leth)	
Lymphocytes	4 (57%)	0 (0%)	0 (0%)	7
Anorexia	1 (14%)	0 (0%)	0 (0%)	7
Dyspnea	2 (29%)	0 (0%)	0 (0%)	7
Mood	1 (14%)	0 (0%)	0 (0%)	7
Weight loss	1 (14%)	0 (0%)	0 (0%)	7
Other endocrine	1 (14%)	0 (0%)	0 (0%)	7
Maximum toxicity	4 (57%)	0 (0%)	0 (0%)	7

Table 3a

Best response to chemotherapy (cycles 1–2).

Best response	# of patients (%)
Partial response	3 (27%)
Stable disease	7 (64%)
Unevaluable ^a	1 (9%)
Overall response rate	27%
95% confidence interval	(6%, 61%)

^aPer study chair review patient 74581 had no post-chemotherapy thoracotomy.

Table 3b

Best overall response to treatment.

Best response	# of patients (%)
Complete response	4 (36%)
Partial response	3 (27%)
Stable disease	3 (27%)
Progressive disease	1 (9%)
Complete response rate	36%
95% confidence interval	(11%, 69%)
Overall response rate	64%
95% confidence interval	(31%, 89%)

Table 4

Overall survival and failure-free survival statistics.

	# patients	# failures	Median (95% C.I)	1-Year (95% C.I)	2-Year (95% C.I)
Overall survival	11	8	17.8 (10.3, ∞)	64% (41%, 99%)	27% (10%, 72%)
Failure-free survival	11	10	8.3 (7.7, ∞)	36% (17%, 80%)	9% (1%, 59%)