Phase II Trial of Combined Modality Therapy with Myeloid Growth Factor Support in Patients with Locally Advanced Non-small Cell Lung Cancer

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Introduction: To evaluate the efficacy and safety of myeloid growth factors in patients with locally advanced non-small cell lung cancer treated with combined modality therapy (CMT).

Methods: Patients with stage IIIA/B non-small cell lung cancer, performance status 0 to 1, and forced expiratory volume in 1 second ≥1.5, received cisplatin 75 mg/m^2 on day 1 + etoposide 80 mg/m^2 on days 1 to 3 every 3 weeks for 2 cycles concurrent with thoracic radiotherapy to 61 Gy. filgrastim 5 mcg/kg/d was administered for 10 days beginning on day 4 of each chemotherapy cycle. Patients without progression received docetaxel 75 mg/m^2 every 21 days for 3 cycles with peg-filgrastim 6 mg on day 2. The primary end point was a 50% reduction in the incidence of grade ¾ neutropenia compared with historical controls.

Results: A total of 26 eligible patients were enrolled. Median age was 67, 76% were men, and 58% had stage IIIA. Gr3/4 neutropenia during CMT was 19.2% and 3.8%, respectively. There were no episodes of febrile neutropenia. Gr4 thrombocytopenia was 15.4% with 2 patients requiring transfusions. Gr3 esophagitis was noted in 7.7% and Gr ¾ pneumonitis in 21.6% of patients. No patients died of treatment-related toxicities. Dose reductions/delays occurred in 3.8% of patients during CMT. Median progression-free survival and median survival were 10.7 and 27.6 months, respectively. The 1- and 2-year survival rates were 61.5% and 46.2%, respectively.

Conclusions: Our data suggest that the addition of filgrastim to CMT is safe and effective. The rate of grade ¾ toxicities, including febrile neutropenia, compares favorably to previous trials using a similar regimen. Dose intensity is maintained. This strategy merits further evaluation.

Key Words: Combined modality therapy, Myeloid growth factors, Stage III NSCLC.

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Approximately 35% of patients diagnosed with non-small cell lung cancer (NSCLC) have locally advanced disease at presentation. The standard of care in this setting is combined modality therapy (CMT), with chemotherapy (CT) and thoracic radiotherapy (TRT) delivered concurrently. Outcomes include a median survival of 18 to 24 months, with approximately 15 to 30% of patients expected to achieve long-term disease-free survival.[1]

One of the principal toxicities of CMT is myelosuppression. Neutropenia is common and often severe, leading to febrile episodes, hospitalizations, and occasionally death. Furthermore, neutropenia may lead to dose reductions and/or dose delays, which may compromise therapeutic outcome in a potentially curable setting. In patients with advanced disease, these complications can be mitigated by the use of myeloid growth factors, such as filgrastim and peg-filgrastim.[2] However, these agents are not approved for use in combination with TRT.

A previous phase III randomized trial by the South West Oncology Group (SWOG) in limited-stage small-cell lung cancer tested CT and TRT with or without sargramostim (granulocyte-macrophage colony stimulating factor), and showed worse thrombocytopenia and more frequent nonhematological adverse events (including toxic deaths) in the growth factor arm.[3] This observation supported early theoretical concerns that growth factors may release megakaryocytes that are more radiosensitive than nonrecruited marrow progenitors.[2] Since then, the use of myeloid growth factors has not been permitted during CMT and has not been revisited despite significant improvements in TRT techniques and supportive care over the last decade.

At the time this study was conceived, a phase II trial by SWOG had shown unprecedented results in patients with stage IIIB NSCLC treated with cisplatin and etoposide concurrently with TRT followed by three cycles of consolidation docetaxel.[4] Hematologic toxicity included grade ¾ neutropenia in 74% of the patients, including two infection-related deaths. A subsequent phase III trial by the Hoosier Oncology Group (HOG), using the same CMT, showed no benefit and worse toxicity for consolidation docetaxel.[5] Grade ¾ neutropenia and febrile neutropenia rates during CMT were 32% and 9.9%, respectively. In both trials, myeloid growth factors were not allowed during CMT.

Therefore, measures to diminish neutropenia would facilitate the delivery of CMT and maintain dose intensity, avoiding important clinical complications and possibly leading to better outcomes. The main objective of this trial was to determine the safety and efficacy of the addition of filgrastim to CMT and peg-filgrastim to consolidation CT.

PATIENTS AND METHODS

Eligibility

Patients with histologic or cytologic confirmation of unresectable stage IIIA/B NSCLC, defined as: N2 disease by biopsy, PET-avidity, or nodes > 2 cm; N3 disease by biopsy, PET-avidity, or contralateral/supraclavicular nodes > 2 cm; T4 disease by documentation of invasion of adjacent structures by radiologist or surgeon. Additional eligibility criteria included performance status 0–1; measurable disease; forced expiratory volume in 1 second (FEV-1) ≥ 1.5 L or if <1.5 L, a predicted FEV1of the contralateral lung of >800 ml based on the quantitative split function testing; and adequate bone marrow, kidney and liver function. Patients with were excluded if they had prior CT or radiotherapy; malignant pleural or pericardial effusion; previous malignancy other than basal or squamous carcinoma of the skin or carcinoma in situ of the cervix, or any other cancer for which the patient had been disease free for 5 years. Patients eligible for consolidation had to have completed CMT within 4 to 8 weeks and have achieved stable disease, partial or complete response and maintain same requirements as the initial eligibility. The study was approved by the Institutional Review Board and all patients signed informed consent.

Treatment Plan

Patients were treated with cisplatin at 75 mg/m^2 on days 1 and 22, and etoposide 80 mg/m^2 on days 1 to 3 and 22 to 24, after appropriate hydration and antiemetics. Filgrastim was administered at a dose of 5 mcg SC daily on days 4 to 13 and 25 to 34. TRT was given as 1.8 Gy daily to 41.4 to 45 Gy to initial fields, followed by a boost to a total dose of 61 to 61.4 Gy beginning on day 1 (Figure 1). The initial radiation field was delivered to a volume that included the primary tumor, ipsilateral hilar nodes, and the ipsilateral mediastinal nodes according to the location of the primary. Elective treatment of supraclavicular nodes was not allowed initially, though the trial was later amended to permit elective supraclavicular radiotherapy at the discretion of the treating radiation oncologist. The boost volume included the primary tumor and known involved lymph nodes measuring ≥1 cm on initial CT plus a 1.5 to 2 cm margin. No more than 35% of total lung volume, minus the primary tumor and lymph nodes greater than 1 cm in diameter, received more than 20 Gy. CT-planning was required, but intensity-modulated radiotherapy was not permitted on the trial.

Patients were reevaluated between 4 and 6 weeks after CMT. Those without progression were treated with consolidation docetaxel at 75 mg/m^2 every 3 weeks for 3 cycles. Peg-filgrastim was administered at a dose of 6 mg SC on day 2 of each cycle.

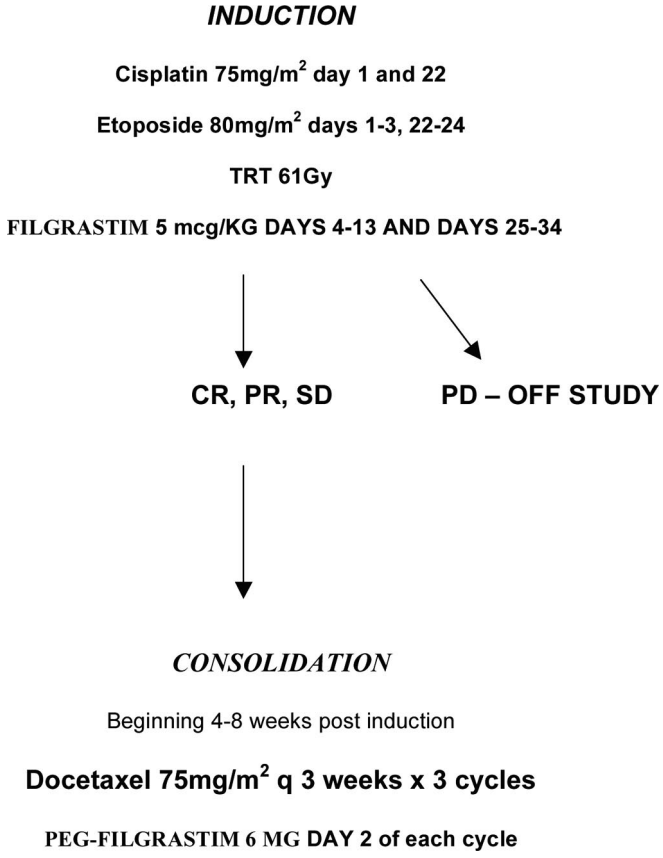

FIGURE 1. Treatment schema.

Dose modifications were permitted once during CMT to cisplatin 60 mg/m^2 and etoposide 60 mg/m^2/d, and twice during consolidation to 60 mg/m^2 and 45 mg/m^2 for febrile neutropenia, grade 4 neutropenia lasting longer than 7 days, grade 4 thrombocytopenia, grade 4 emesis, grade ≥3 diarrhea, grade 2 neuropathy, grade 3 fluid retention, abnormal liver function, and grade ≥3 stomatitis. Treatment was delayed for grade ¾ toxicity until it resolved to at least grade 1, then reinitiated with one dose level reduction. Response criteria were evaluated according to the RECIST criteria.

Statistical Design

The primary end point was the incidence of grades 3 and 4 neutropenia during CMT and consolidation CT. Assuming a 74% incidence of grades 3 to 4 neutropenia in the historical control (SWOG 9504), with a power of 90%, approximately 28 patients were needed to detect a 50% reduction in grades 3 to 4 neutropenia. The key secondary endpoints were incidence of grade 4 thrombocytopenia; incidence of toxic deaths caused by thrombotic/embolic events or pneumonitis; and incidence of grade ¾ esophagitis, as observed in the historical control (SWOG 9504), with 0%, 2% and 17%, respectively. Efficacy parameters included response rate after CMT and after consolidation, progression-free survival, median, and 1-year survival. The progress of the study with an emphasis on safety analysis was monitored by the principal investigators and reported on a regular basis to the

institutional review board. Appropriate safeguards were in place to monitor toxicities throughout the conduct of the trial. The study was to be terminated if 3 of 10 or >6 of 20 subjects had grade 4 thrombocytopenia requiring platelet transfusion, or if 1 of 10 or >2 of 20 subjects had toxic deaths caused by thrombotic/embolic events or pneumonitis other severe unexpected toxicities.

RESULTS

Patient Characteristics and Treatment Compliance

Twenty-six patients were enrolled between March 2004 and March 2009. Accrual became difficult after the publication of the HOG trial and the principal investigators decided to close the study because of ethical concerns about the template regimen. Patient characteristics are shown in Table 1. Median age was 67 (range, 50–81), 76% were men, and 38% had performance status 0. Fifteen patients had stage IIIA and 11 had stage IIIB disease. Histologic subtype revealed 42.3% adenocarcinoma. All patients had FEV1 ≥ 1.5 L and all had a PET scan at baseline.

All patients completed CMT with 2 dose delays and 1 dose reduction as per protocol. Of the 23 patients treated with at least one cycle of consolidation docetaxel, 14 received all 3 cycles; 8 received 2 cycles; and 1 received 1 cycle. Three patients had progressive disease after CMT and did not receive consolidation. Reasons for discontinuation of docetaxel were grades 2 and ¾ pneumonitis in 4 and 2 patients, respectively, in whom the third cycle of consolidation was withheld; and fluid retention in one patient.

Toxicity

The main toxicities are summarized in Table 2. During CMT, grade 3 neutropenia was observed in five patients (19.2%), whereas one patient (3.8%) had grade 4 neutropenia. No patient had febrile neutropenia. Grade 4 thrombocytopenia was noted in 4 patients (15.4%), with platelet counts ranging from 9,000 to 24,000. Two patients required a platelet transfusion. No bleeding was observed. Grade 3 anemia was noted in two patients (7.7%) and two required transfusions. Nonhematologic toxicities during CMT were mild to moderate, including grade 3 esophagitis in two patients (7.7%).

Among the 23 patients treated with consolidation docetaxel, hematologic toxicity was mild, with only one episode of grade 3 anemia but no grade ¾ neutropenia or thrombocytopenia. Pneumonitis was grade 3 in four patients (17.3%), and grade 4 in one patient (4.3%). No patient died of treatment-related toxicities.

TABLE 1. Patient Characteristics

	Total (n = 26)
Gender	
Male	20 (76%)
Female	6 (24%)
Age, median (range)	67 (50–81)
Age, ≥70	9 (35%)
Histological type	
Adenocarcinoma	11 (42%)
Others	15 (52%)
ECOG performance status	
0	10 (38%)
1	16 (62%)
Stage of disease	
IIIA	15 (58%)
IIIB	11 (42%)

TABLE 2. Selected Grade 3/4 Toxicities

	CMT (n = 26)	Consolidation (n = 23)
Hematological toxicities		
Neutropenia	6 (23%)	0
Anemia	2 (7.7%)	1 (4.3%)
Thrombocytopenia	4 (15.3%)	0
Non-hematological toxicities		
Pneumonitis	0	5 (21.6%)
Esophagitis	2 (7.7%)	0
Fluid retention	0	1 (4.3%)
Infection, sepsis, FN	0	0
Dose adjustments (reductions/delays)	3 (11.5%)	13 (50%)

CMT, combined modality therapy.

TABLE 3. Efficacy Parameters

	CMT/Consolidation (n = 26)
Best response (%)	58
Median PFS (months)	10.7
Median survival (months)	27.8
1-yr survival (%)	61.5
2-yr survival (%)	46.2

PFS, progression-free survival.

Efficacy

Response after CMT for all 26 eligible patients (intention to treat) was 57.5% (95% CI, 37.9–76) (Table 3). Among the 23 patients treated with consolidation docetaxel, the response rate was 56.5% (95% CI, 36.9–75.1). Three patients had progressive disease after CMT and were not evaluable for response after consolidation. For all 26 eligible patients, median progression-free survival was 10.7 months (95% CI, 5.36–16), and median survival was 27.8 months (22.1–33). The 1- and 2-year survival rates were 61.5% (95% CI, 42.2–79.7), and 46.2% (95% CI, 26.8–65.2), respectively.

DISCUSSION

To our knowledge, this is the first trial in NSCLC that evaluates the use of myeloid growth factors in patients receiving CMT. Our study demonstrates that the addition of filgrastim to CT and TRT is safe and effective. The rates of grade ¾ neutropenia and febrile neutropenia are significantly reduced compared with prior trials using an identical regimen. For example, in SWOG 9504, grade ¾ neutropenia was reported in 74% of patients, including two infection-related

deaths.[4] In the more recent HOG trial, during chemoradiotherapy, grade ¾ neutropenia and FN were reported in 32% and 10% of patients, respectively.[5] Finally, in a more recent SWOG trial (SWOG 0023), using the same concurrent regimen, grade ¾ neutropenia was noted in 43% of patients.[6] Information on dose adjustments was not reported in these studies. In our study, dose intensity was preserved, and no deaths occurred as a consequence of CMT.

We observed grade ¾ thrombocytopenia in 15% of patients, which is high, but still within the range observed in other studies, such as 7% in SWOG 9504, 11% in the HOG trial, and 10% in SWOG 0023. Two patients required a transfusion, but none had significant bleeding. Although it is possible, and perhaps likely, that mobilization of marrow precursors by filgrastim may lead to higher rates of thrombocytopenia, this toxicity, when properly monitored, appears to be largely without serious clinical consequences and, in our opinion, does not negate the benefits of filgrastim in the rates of neutropenia and infection. Our rate of esophagitis was also comparable to previous studies, suggesting no obvious adverse interaction between the growth factor and this complication.

However, our rate of pneumonitis during consolidation was worrisome. Although a contribution from with pegfilgrastim cannot be excluded, it is unlikely. The rate of pneumonitis with consolidation docetaxel was lower in the HOG trial and the SWOG 0023 trial. Many patients were unable to complete the prescribed three cycles of consolidation and dose adjustments were frequent. Hence, pneumonitis appears to be an inherent complication of consolidation docetaxel after CMT and does not seem to have been altered substantially by the use of growth factors. However, we cannot conclusively exclude such a contribution. Because all our patients had an acceptable FEV1, we could not correlate the incidence of pneumonitis with borderline lung capacity.[7] As explained above, by the time our trial was designed, the SWOG regimen seemed as a logical choice to test our hypothesis. Since then, consolidation docetaxel after CMT has been shown to offer no benefit.

The most likely reasons for our favorable experience, in contrast to the original SWOG trial, are potential differences between filgrastim and sargramostim as first, and significant improvements in TRT techniques achieved over the last decade as second. Sargramostim was used in the original SWOG trial and has broader action on precursor cells than filgrastim, particularly with respect to macrophages, which may account for a greater incidence and severity of inflammatory processes, such as esophagitis and pneumonitis. However, any significant clinical differences that may exist as a result of these biologic differences, particularly when used in combination with TRT, remain hypothetical and yet to be proven in the clinical arena.[8] Innovations in TRT, including dose, fractionation, planning, and target determination have been substantial and arguably the single most significant advance in the management of stage III NSCLC since the principles of CMT were laid out in the early to mid-1990s. These improvements allow for a more precise treatment volume, therefore minimizing potential negative interactions between radiation and myeloid precursors.[9]

Although our study used a cisplatin/etoposide regimen, our findings are of potential application to patients with locally advanced NSCLC treated with other CT regimens and TRT. Moreover, it is conceivable that our findings can be extrapolated to other locally advanced malignancies treated with combined CT and radiotherapy, and additional studies are encouraged. Indeed, based on our experience, the RTOG-activated a phase II trial to test the use of filgrastim with CMT in patients with limited-stage small-cell lung cancer, where dose intensity may play a more relevant role (RTOG 0623). The trial, however, has been closed because of lack of accrual and competition with the ongoing phase III intergroup trial.

In summary, despite the small size of the trial, our experience suggests that the use of myeloid growth factors safely abrogates neutropenia and its complications and maintains dose intensity during CMT in patients with locally advanced NSCLC. This strategy merits consideration as an adjunct to clinical trials in patients undergoing CMT.

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