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.

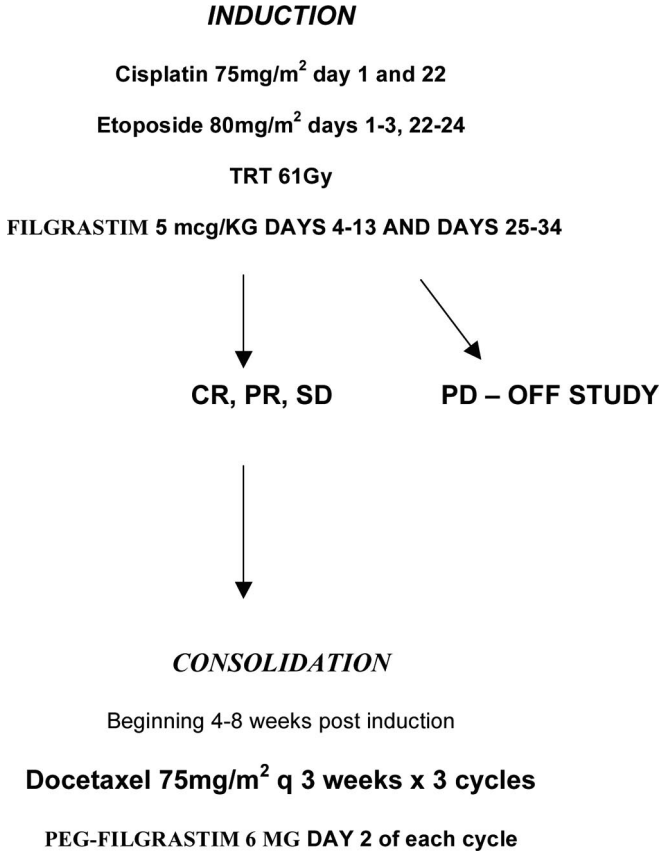

FIGURE 1. Treatment schema.

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