Induction Chemotherapy Followed by Chemoradiotherapy Compared with Chemoradiotherapy Alone for Regionally Advanced Unresectable Stage III Non-Small-Cell Lung Cancer: Cancer and Leukemia Group B

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Background

- Standard therapy currently for unresectable stage III NSCLC is concomitant chemoradiotherapy (CRT)
- CALGB 39801 asked the question whether induction chemotherapy before concurrent CRT would result in improved survival
- Historical perspective:
    - After Dillman study (CALGB 8433), French CEBI 138 study (Le Chevalier *et al* 1991) and RTOG 8808 study (Sause *et al*), chemotherapy has been routinely added to radiotherapy (RT) for unresectable Stage III patients. Subsequently it was demonstrated that concurrent chemoradiotherapy is superior to sequential chemoradiotherapy (chemotherapy followed by radiotherapy) (Three studies: RTOG 9410, NPC 95-01 and Furuse *etal)*
    - Concurrent CRT hence became established practice.
    - What about induction chemotherapy followed by CRT, would that give better systemic control without losing the advantage of better locoregional provided by concurrent CRT? Can we make the survival rate even better?
    - A series of phase II studies demonstrated the above scheme was feasible, and Median Survival (MS) achieved was similar to that for concurrent CRT and better than sequential CRT.

Patients (pt) and Methods

- Accrual period 7/1998-5/2002
- Histologic /cytologic documentation of NSCLC.
- Previously untreated unresectable tumor or inoperable Stage III disease.
- Excluded pt with scalene, supraclavicular or contralateral hilar nodes, direct invasion of the vertebral body or with a pleural effusion.
- N3 disease OK as long as all gross disease can be encompassed in the radiation boost field.
- Wt loss of > or = 5% in the 3 mo before diagnosis OK
- All patients have assessable/measurable disease
- CALGB performance status of 0-1, life expectancy> 2mo, Age>18, no pregnancy
- FEV1>800cc

- All pt got standard lab tests pretreatment, CT or MRI of chest and upper abdomen (Adrenal and liver included) and bone scan

Treatment Plan

- Arm A : after registration and randomization, pt received Paclitaxel 50 m/m 2 IV/1h/wk, Carboplatin AUC 2 IV/30 min/wk for 7 cycles (7 weeks) and XRT 66 Gy in 2 Gy fractions (Concurrent CRT)
- Arm B : after registration and randomization, pt initially received Paclitaxel 200 mg/m 2 IV/3h, Carboplatin AUC 6 IV/30min every 21 days for a total of 2 cycles then receive the identical treatments as Arm A (Paclitaxel 50 m/m2 IV/1h/wk, Carboplatin AUC 2 IV/30 min/wk for 7 cycles (7 weeks) and XRT 66 Gy in 2 Gy fractions)

Chemotherapy and Dose modifications

- -dose adjusted for low platelet counts and/or granulocytes
- -dose adjusted for >grade 3 neurotoxicity
- -dose adjusted for >grade 3 esophagitis, mucositis, stomatitis and dermatitis

RT

- Arm A started on day 1, Arm B started on day 43;
- Beam energy 4-25 MV
- Target Volume:
  - *Original volume (OV)* : based on a planning CT prior to chemo; including the primary lesion, grossly involved nodal sites, plus ipsilateral hilum and mediastinum with a margin of 2cm
  - *Boost volume (BV)* : all sites of gross disease, ipsilateral hilum and reduced ipsilateral mediastinum; excluded the spinal cord; <50% ipsilateral lung volume
- Both 2- and 3-D treatment planning systems OK.
- Dose: OV 44 Gy in 22 fractions of 2 Gy/fraction; Boost volume was 22 Gy in 11 fractions. Max dose to spinal cord was 49 Gy.
- -Central QARC.

Statistics

The trial was designed to have 80% power to detect a 40% increase in median survival, from about 13mo to 18.2 mo with the addition of induction chemo using a one-tailed log-rank test conducted at a 0.025 level of significance.

Results

- N=366, (161 and 170 in arm A and B respectively)
- Pt characterisits are similar between the two arms (Table 1)
- Toxicity from induction chemo alone (Table 2) showed grade 3 and 4 granulocytopenia (18% and 20%); and Max toxicity was grade 3 (31%) and grade 4 (23%)
- Toxicities from concurrent CRT (Table 3) showed greatly increased neutropenia on Arm B. Other toxicities were not significantly different.
- Survival: No significant difference with median follow-up time of 38 months
  - MS: 12 mo vs 14 mo
  - 2 year: 29% vs 31%
  - 3-year: 19% vs 23%
  - FFS also not significantly different: 7 mo vs 8 mo

- When pt who were cancelled or ineligible were excluded (i.e. not using Intent-to-treat protocol), N=331, re-analysis did not change the conclusion, but favored Arm B.
    - MS 12 mo vs 14 mo, favoring arm B (P=0.2)
- When pts with greater weight loss were included (Previously this pt population was excluded in other CALGB trials)?
    - N=244, MS 16mo vs 14mo (P=0.9) favoring arm A

Author's Conclusion

- Addition of induction chemotherapy does not provide a survival benefit over concurrent therapy alone.
- There is also increased risk of neutropenia and overall maximal toxicity with the addition of induction chemotherapy.
- The survival times in the study are disappointing (MS 12 mo and 14 mo).
- Author argues that different chemo agents like cisplatin and etoposide or cisplatin and vinblastine may well be better than paclitaxol and carboplatin considering the latter agents involve a significant attenuation of dose during radiation.- this may explain the disappointing survival data.
- The study included pts with weight loss >5%, which may be a poor prognostic factor, independent of performance status, thus adversely affected the outcome.
- Significant proportion of pt failed to receive RT as intended in the trial, although it did not make significant difference when these pt were excluded.

Comments

- This is a well-designed clinical trial demonstrating adding induction chemotherapy agents Paclitaxol and carboplatin prior to concurrent CRT does not add survival benefit, but increases toxicity such as neutropenia.