Selected Summary (II)

Adjuvant Chemotherapy In Completely Resected Non-Small- Cell Lung Cancer

International Adjuvant Lung Cancer Trial Collaborative Group

Cisplatin-Based Adjuvant chemotherapy in Patients with Completely resected Non-Small-Cell Lung Cancer.

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SUMMARY

The role of Adjuvant chemotherapy in completely resected Non-Small-Cell lung cancer is not clear despite a number of randomized controlled trials over the years. A meta-analysis[1] earlier has suggested that cisplatin based adjuvant chemotherapy could yield an absolute overall survival advantage of 5 percent at five years. The main objective of this study was to compare the effect on overall survival of adjuvant chemotherapy consisting of cisplatin plus a vinca alkaloid or etoposide with that of no adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer.

The study was conducted in 148 centres across 33 countries. Each centre chose its chemotherapy options before the study began. Cisplatin at doses varying from 80-120mg/m^2 for 3-4 cycles every 21-28 days were combined with either vinca alkaloids(vindesine 3mg/m^2 or vinblastine 4 mg/m^2 or vinorelbine 30 mg/m^2) weekly or etoposide 100 mg/m^2 for 3 days with each dose of cisplatin. Postoperative radiotherapy, when delivered ,was given after completion of chemotherapy, in chemotherapy group. The eligible patients were between 18-75 years of age, had pathologically documented non-small –cell lung cancer of stage I, II, or III, and had undergone complete resection. No prior chemotherapy or radiotherapy was allowed, and had no previous malignancy. They were randomly assigned to the adjuvant –chemotherapy group or control group through a centralized randomization system at Institut Gustave-Roussy in France. In the chemotherapy group, the assigned treatment was to start within 60 days after surgery and within 14 days after randomization.

The primary end point was overall survival after randomization. Secondary end points were disease free survival, second primary cancers, and adverse effects. All analyses were performed strictly according to the intention – to-treat principle and included all randomized. Cox model was used for analyses.

A total of 1867 patients underwent randomization from february 1995 to 31st december 2000. Nine hundred and thirty two patients were randomly assigned to the chemotherapy group and 935 to the control group. Baseline characteristics of the patients were matched in both groups for age, sex, stage, type of surgery, performance status and histological subtype. The most common chemotherapy option chosen was 100 mg/m^2 of cisplatin for 3-4 cycles with etoposide however, 7.8% did not receive chemotherapy. Seven patients died of toxic effects of chemotherapy. Among 572 patients assigned to receive adjuvant thoracic radiotherapy, 70.4% of those in the chemotherapy group and 84.2 %in the control group received this treatment.

Among the 1867 randomized patients , 973 died : 469 in the chemotherapy group and 504 in the control group. The five year survival rates were 44.5% in the chemotherapy group and 40.4% in the control group ($p<0.03$).There were 518 events (disease progression or death)in the chemotherapy group and 577 in the control group. The disease- free survival rate was significantly higher in the chemotherapy group($p<0.003$).

Comment

Role of adjuvant chemotherapy in completely resectable non- small cell lung cancer is unclear and debatable as per recommendations of

American College of Chest Physicians and the results of meta-analysis which showed 5% absolute improvement in survival with cisplatin based chemotherapy but failed to reach statistical significance.[1,2] Therefore conclusions of the above study may not be entirely significant. Subset analyses of patients did not show significant difference in deaths between the two arms in Stage I and II. However, modest improvement in overall survival was seen in Stage III. Similarly PORT meta analysis has shown that adjuvant radiotherapy is deleterious in completely resected Stage I and II tumors and did not improve survival in Stage III patients[3]. Therefore in the present study benefits of chemotherapy may be an overestimation, as increased number of deaths in control group may have been because of radiotherapy as more patients in control group received radiotherapy.

Recently trials using neoadjuvant chemotherapy followed by surgery have shown improved survival compared to surgery alone in resectable stage III disease.[4,5] However limitation of these studies has been small number of patients. Therefore randomized trials comparing neo adjuvant and adjuvant chemotherapy with newer drugs like paclitaxel, carboplatin, and gemcitabine may find best multimodality approach in lung cancer.

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