Poster Session

Lung cancer

768 POSTER

Efficacy of oral UFT for adjuvant chemotherapy after complete resection of non-small cell lung cancer: Meta-analysis of six randomized trials in 2003 patients

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Background: Clinical trials assessing the response of non-small-cell lung cancer to postoperative adjuvant chemotherapy should use survival as the primary endpoint. Response should be evaluated by means of randomized controlled studies using surgical therapy alone as control. Single studies usually do not provide clear-cut conclusions because of limited sample size. We therefore performed a meta-analysis of all properly randomized clinical trials comparing long-term adjuvant chemotherapy with UFT, an oral fluorinated pyrimidine derivative, with surgery alone in patients with completely resected non-small-cell lung cancer.

Material and methods: Six such trials were identified.

1) The Japan Lung Cancer Research Group
2) The West Japan Study Group for Lung Cancer Surgery(II)
3) The West Japan Study Group for Lung Cancer Surgery(IV)
4) North-east Japan Study Group for Lung Cancer Surgery
5) Osaka Lung Cancer Study Group
6) Adjuvant Chemotherapy for Lung Cancer Study Group

The analysis was based on individual patient data provided by the principal investigator of each trial. Data from 2003 eligible patients were analyzed on an intention-to-treat basis. The endpoint of interest was overall survival at 5 years after surgery. Major prognostic factors were well balanced between the UFT group and surgery alone group. Most patients had early-stage non-small-cell lung cancer, pT1(65%) and pT2(34%).

Results: The results of meta-analysis demonstrated that adjuvant chemotherapy with UFT improved overall survival (hazard ratio, 0.77; 95%CI, 0.63-0.94; p=0.011). The difference in the 5-year survival rate between the UFT arm (81.8%) and surgery alone arm (77.2%) was 4.6%. Heterogeneity of effect among the six studies was not significant (p=0.76).

Conclusion: On the basis of our meta-analysis, we conclude that postoperative adjuvant chemotherapy with UFT has a beneficial effect on outcome in patients with curatively resected non-small-cell lung cancer.

769 POSTER

Reducing health care burden for the treatment of toxicity associated with pemetrexed or docetaxel in patients with advanced non-small cell lung cancer who previously received chemotherapy: application to the UK setting

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Introduction: Management of toxicities associated with cytotoxic chemotherapy contributes to the burden of the UK National Health Service (NHS) of providing health care to patients (pts) with advanced non-small cell lung cancer (NSCLC). This preliminary analysis summarises incidence and costs of some of the most expensive toxicity-related supportive care for two treatments for NSCLC.

Methods: This economic assessment was based on resource utilisation data collected prospectively in a multinational, phase III randomised study comparing pemetrexed (pem) with docetaxel (doc) in pts with NSCLC who had previously received chemotherapy. We evaluated the direct medical costs of key investigator-determined drug-related adverse events (AEs) reported for these two treatment groups. Data included in this initial analysis were hospitalisations (both admissions and days), transfusions, erythropoietin, granulocyte colony-stimulating factors (GCSFs) and parenteral antibiotics. Unit costs were sourced from UK NHS casemix data (published in 2002) and UK national drug prices. Costs were calculated as mean cost per pt.

Results: Baseline pt and disease characteristics from the 541 pts who received treatment were well balanced. Results of the trial demonstrated similar median survival time and tumour response rates for both arms (approximately 8 months and 9%, respectively). The mean number of cycles administered was 4.4 on the pem arm and 3.9 on the doc arm. D rug-related serious AEs were significantly higher for doc compared with pem (24% vs 10%). CTC grade 3/4 neutropenia and neutropenic fever were significantly higher in the doc arm (40% vs 5%, 13% vs 2%, respectively). Most other grade 3/4 toxicities, including nausea/vomiting, thrombocytopenia and anemia, were similar between treatment arms and occurred at low rates (≤5%). Although more pts on the doc arm received erythropoietin, more pts on the pem arm received red blood cell transfusions. Pts on the pem arm received fewer courses of parenteral antibiotics (106 vs 151) and GCSF (10 vs 100) and required fewer hospital admissions (21 vs 72) and days (160 vs 346). The most common reason for drug-related hospitalisation for both arms was febrile neutropenia (4 admissions in the pem arm vs 43 in the doc arm). Cost results (mean cost per pt) were as follows:

	Pemetrexed (N=265)	Docetaxel (N=276)
Total hospitalisations	£154	£408
Outpatient transfusions	£2	£0
Erythropoietin	£61	£70
GCSF	£13	£128
Parenteral antibiotics	£9	£12
Total	£239	£618

Conclusions: For patients with advanced NSCLC who have previously received chemotherapy, pemetrexed offers similar survival and response rates with a more favourable toxicity profile relative to docetaxel. In the management of chemotherapy-related adverse events, pemetrexed is less expensive and requires fewer unscheduled supportive care interventions, thus reducing the NHS health care burden.

770 POSTER

Final results of phase II trial of s-1 plus cisplatin (CDDP) in patients with non-small-cell lung cancer (NSCLC)

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Background: 5-Fluorouracil (5-FU) is one of the widely used therapeutic agents for solid tumors. However, its usefulness is limited by dihydropyrimidine dehydrogenase (DPD), which rapidly inactivates 5-FU. To enhance therapeutic activity, two new oral 5-FU derivatives combined with DPD inhibitors, UFT and S-1,have been developed. UFT consists of 1 M tegafur (a prodrug of 5-FU) and 4 M uracil (a DPD inhibitor) and has been approved in 60 countries. UFT plus CDDP is effective against NSCLC with a response rate (RR) of 29.1%. S-1 consists of 1 M tegafur, 0.4 M gimeracil (a potent DPD inhibitor), and 1 M potassium oxonate, which selectively decreases gastrointestinal toxicity. S-1 is now widely used for the management of

advanced gastric and head and neck cancers in Japan. S-1 has been shown to be active against NSCLC, producing a RR of 22.0% when given as monotherapy (Kawahara et al. Br J Cancer 2001). A combination of CDDP and S-1 is superior to S-1 alone in vivo. We evaluated the response and safety of combination chemotherapy with S-1 plus CDDP in patients with NSCLC.

Patients and Methods: The eligibility criteria were as follows: Stage IIIB or IV NSCLC, confirmed histologically or cytologically; a performance status of 0 to 2; an age of ≤74 years; adequate organ functions; and no prior chemotherapy. Written informed consent was obtained from all patients. S-1 was administered orally at 40mg/m^2 twice daily for 21 consecutive days. CDDP (60mg/m^2) was administered intravenously on day 8 of treatment with S-1. This cycle was repeated every 4 to 5 weeks, depending on toxicity.

Results: Of the 56 patients enrolled, 55 were eligible. The median number of administered cycle was 3 (range 1-12). The overall response rate was 47% (95% CI: 34%-61%, 1 CR and 25 PR). Survival has been good and is under further analysis. Toxicity was generally mild to moderate. Dose-limiting toxicity was hematological: grades 3 and 4 neutropenia (29%) and anemia (22%). Grade 3 non-hematological toxicity comprised anorexia(13%), vomiting(7%), and diarrhea(7%). There was no Grade 4 non-hematological toxicity.

Conclusions: Combination chemotherapy with S-1 plus CDDP is very effective and well tolerated in patients with advanced NSCLC. Because the need for hospitalization is minimal, this regimen is likely to improve the quality of life of patients. These results warrant further investigations of S-1 plus CDDP, including a randomized controlled trial as first-line treatment in NSCLC.

771 POSTER

Paclitaxel and carboplatin as adjuvant treatment in high-risk patients with operable non-small cell lung cancer (NSCLC): A feasibility study conducted by the Hellenic Cooperative Oncology Group (HeCOG)

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Background: The use of adjuvant chemotherapy in operable NSCLC is still under investigation. The combination of paclitaxel and carboplatin has been proved an active, safe and convenient regimen for the management of advanced disease.

Material-Methods: From 1/7/1998 to 2/9/2002, 75 patients with IB-IIIA completely resected NSCLC entered the HeCOG protocol HE 2C/98. They were treated with paclitaxel 175mg/m2 and carboplatin at an AUC of 6 every 3 weeks for 6 cycles. Patients with stage IIIA also received adjuvant RT to the mediastinum after completion of chemotherapy.

Results: There were 62 (83%) men and 13 (17%) women with a median age 63 years (range, 44 - 76) and median PS 0 (range, 0 - 2). Stage IB included 16 patients, stage II 25 patients and stage IIIA 34 patients. Fifty-eight patients (77%) completed all cycles of treatment. Median relative dose intensity of paclitaxel was 1.00 (range, 0.7 – 1.2). Median cumulative dose of carboplatin was 3305mg (range, 500 – 5640). Most commonly seen toxicities included anemia (31%), leukopenia (13%), nausea/vomiting (26%), myalgias/ arthralgias (56%), peripheral neuropathy (75%). Expression of COX-2, VEGF, cyclin D1, DDH and RCAS-1 were assessed immunohistochemically. The prognostic significance of the above mentioned markers on relapsed-free survival and overall survival will be presented at the meeting.

Conclusions: The combination of paclitaxel and carboplatin given post-operatively in high-risk patients with NSCLC is a well-tolerated, safe and convenient regimen.

772 POSTER

Comparison of two Cisplatin based doublets (Gemcitabine/ Cisplatin, Etoposide/ Cisplatin) in advanced non-small cell lung cancer

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Background: Despite the poor prognosis of patients with advanced non-small cell lung cancer (NSCLC), treatment with the new generation chemotherapy agents has improved survival and quality of life, and decreased toxicity compared to older Cisplatin based doublets. The aim of this study is to assess, in a randomized phase II trial, the results obtained in advanced stage (st) i.e. IIIB and IV NSCLC patients (pts) with a 3rd generation platinum doublet Gemcitabine/ Cisplatin (GP) versus the 2nd generation Etoposide/ Cisplatin (EP) regimen.

Methods: From 10/96 to 10/02, 88 previously untreated pts received either GP (Gemcitabine 1250 mg/m^2 d1, 8, Cisplatin 80 mg/m^2 d1), or EP (Etoposide 120 mg/m^2 d 1-3, Cisplatin 80 mg/m^2 d1) q3wks. St IIIB pts without pleural effusion had 3 cycles (cyc) followed by RT at 60 Gy; st. IV and st IIIB pts with pleural effusion had up to 6 cyc of chemotherapy (less if progressive disease).

Results: 80% males; age 57 [range 39-74]; WHO PS 0&1 in 51 pts, 2 in 37 pts; histology: squamous 56, adeno 24, large cell 4, non-small (cytology) 4 pts; AJCC st: IIIB 42, IV 46 pts; protocol GP 43, EP 45 pts. *Toxicity*: 313 cyc were given (GP 159, EP 154), with one toxic death in EP (renal failure). Febrile neutropenia (gr. 4) occurred (GP vs EP) in 2 vs 7 cycles, gr. 4 anemia 1 cyc in both arms. *Activity*: 27 pts had an objective response to CT (=31%, CI [21%-40%] at 0.05), 2 CR, 25 PR. Response rate was influenced by the PS (0-1 vs 2: 39% vs 19%, p=.04) and was not significantly different in respect with gender, clinical stage or chemotherapy regimen (GP vs EP: 26% vs 36%, p=.31). *Survival* (S): At a median (med) follow-up of 7 months (m) [1-31], overall med S is 7,6 m and 1 year S is 25%. Med S was influenced by the PS (0-1 vs 2: 10.5 vs 7.1 m, p<.01) and response to chemotherapy (CR+PR vs SD+PD: 11.2 vs 6.7 m, p<.01). A significant improvement in med S occurred with GP vs EP (10,3 vs 7.1 m, p=.04, 1-year S 39% vs 14%, p<.05). Only a trend existed among st IIIB vs st IV pts (9.7 vs 7.1 m, p=.20).

Conclusions: 1) There were no significant differences in response among the two platinum doublets. 2) Survival was significantly improved with GP over EP. 3) Prognostic factors found: for response - PS; for survival - PS, response to chemotherapy and regimen.

773 POSTER

Clinical usefulness of tumor marker CYFRA 21-1 in surgical treatment of lung cancer

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Background: Both incidence and mortality of lung cancer increase. Introduction of tumor marker CYFRA 21-1 into clinical praxis improves the inevitable surgical treatment. Aim: Intensification of clinical diagnostics in earlier recognition of tumor biological activity using tumor marker CYFRA 21-1 in both primary diagnosis and relapse; facilitate the choice whether to operate and reoperate in the same stage of disease.

Material and Methods: The sample includes 2947 patients who were surgically treated in our Clinic. 882 non small cell lung cancer (NSCLC) patients of 2947 have been controled in the Clinic for six years (adeno-carcinoma –AD and squamous cell carcinoma -SQC). In order to control disease status, CYFRA 21-1 level has been measured by ECLIA method before therapy and twelve times after the therapy, along with the clinical examinations.

Results: The sensitivity of CYFRA 21-1 in patients with primary lung cancer was 75,51%. Taking into consideration both surgical algorythm and past experience there was a need to incorporate CYFRA 21-1 into algorythm. Patients who had high values of CYFRA 21-1 before therapy (above 12 ng/mL) suffered from relapse within 1 year after the therapy (10,3%). Although CYFRA 21-1 level rises from stage IA to IIIA, we have noticed that patients in early stage with high values have also suffered from relapse earlier. In AD stage IA CYFRA 21-1 relapse has been proven between 18 and 60 months after therapy and clinical relapse between 24 and 60 months after therapy. In AD stage IIIA CYFRA 21-1 relapse was between 4 and 60 months after therapy and clinical between 10 and 60 months after therapy. The highest number of clinically proven relapses was seen between 36 and 42 months after therapy. In early stages of SQC relapses have been proven 6 to 12 months later than in AD. In late stages