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Best of ASCO 2005 in clinical research for lung cancer

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This report reviews the highlights in treatment of non-small and small cell lung cancer, covering clinical results in adjuvant and neoadjuvant settings, combined modalities, and systemic treatment of advanced disease.

NON-SMALL CELL LUNG CANCER (NSCLC)

Adjuvant chemotherapy

In prospective phase III trial (ANITA), 840 patients completely resected for early stage of disease (stage I, T2N0, stage II and IIIA), from 101 centers in 14 countries, were randomized to receive vinorelbin 30mg/m^2/week x 16 plus cisplatin 100mg/m^2 d1 q 4 weeks for 4 cycles. Pneumonectomy was carried out in 37% of patients and lobectomy in 58%. After median follow-up of more than 70 months, median survival was 65.8 months in the adjuvant arm and 43.7 months in observation arm (p=0.0131, HR 1.264). Survival at 2, 5 and 7 years was 68%, 51% and 45% in the adjuvant and 63%, 43% and 37% in the observation arm respectively. The 5-year survival by stage I, II and IIIA were 62%, 52% and 42% in the adjuvant and 63%, 39% and 26% in the observation arm respectively. Both differences were statistically significant. Treatment toxicity was moderate, with 8.5% of febrile neutropenia and nausea/vomiting gr. 3/4 in 27%. Treatment-related death was recorded in 5 patients (1%). The authors concluded that adjuvant chemotherapy vinorelbin-cisplatin significantly improves survival in completely resected stage II and IIIA NSCLC, although no benefit was observed in stage I disease (1).

Neoadjuvant chemotherapy

SWOG reported results of preoperative chemotherapy with most preferable American regimen paclitaxel-carboplatin (study S9900). The planned sample size was 600 patients, but following the positive adjuvant data, S9900 trial was closed to new entry in July 2004 with 354 patients being accrued. Patients with T2N0, T1-2N1, and T3N0-1 (excluding superior sulcus tumors) were randomized to receive 3 cycles of preoperative paclitaxel 225mg/m^2 over 3h and carboplatin AUC 6, or surgery alone. Progression-free survival was 29 months in the chemotherapy arm, and 20 months in surgery only arm (p=0.26) and median survival was 42 months for chemotherapy arm and 37 months for surgery only arm (p=0.47). This negative study is one of the largest randomized trials in neoadjuvant setting, and after plenty of positive adjuvant trials the authors concluded that randomized trials comparing preoperative to adjuvant chemotherapy are warranted (2).

Combined modalities in stage IIIA (N2)

In INT 0139 study, concurrent chemo/radiotherapy was compared with chemo/radiotherapy followed by surgical resection for stage IIIA (N2): initial analyses showed significantly better progression-free survival, but not overall survival in the trimodality arm. Three hundred and ninety-six eligible patients were analyzed, now with longer follow-up (more than 2.5 years per patient): in trimodality arm 16 TRD were recorded (7.9%), 10 of them in first 30 postoperative days, while only 4 (2.1%) in chemo/radiotherapy arm. In progression-free survival, there was a statistically significant difference in stands: 12.8 months for trimodality arm and 10.5 months for chemo/radiotherapy arm (p=0.017), 5-year PFS 22.4% vs. 11.1%. Survival curves overlapped for 2 years but separated later, favoring surgical arm (23.6 vs. 22.2 months, p=0.24). Independent favorable predictors of survival were female gender and no weight loss. N0 status at surgery improved prognosis of such patients: 5-year survival for N0 was 41%, for N1-3 24%. The authors stated that longer follow-up confirmed significantly improved PFS, but not overall survival when surgery follows chemo/radiotherapy (3).

In another study that questioned the role of surgery in N2 patients, EORTC 08941 study, patients were randomized to radical surgery (radical resection with lymph node dissection and optimal postoperative radiotherapy-PORT) versus thoracic radiotherapy (at least 40Gy in 2Gy daily fractions on the mediastinum with a boost to at least 60Gy on the involved fields), but only after response to induction (3 cycles) platinum-based chemotherapy (even SD were excluded!). Among 572 patients who started protocol treatment, 333 patients were randomized (the response rate to induction chemotherapy was 61.5%): 167 to surgery (S) and 166 to thoracic radiotherapy (TRT). After a median follow-up of 72 months, results are as follows: median PFS was 9.0 months in S arm and 11.4 months in TRT arm (p=0.6), median survival was 16.4 months in S arm and 17.5 in TRT arm, 2-year survival 35 vs. 41% and 5-year survival 16 vs. 13%. The conclusion was that in selected patients with proven N2 (IIIA) and a response to induction chemotherapy, surgery improves neither overall survival nor progression-free survival as compared to thoracic radiotherapy (4).

Advanced non-small cell lung cancer

Targeted agents continue to be the center of clinical research in advanced disease, combined with conventional cytotoxic agents, given alone or even in combination with another targeted agent. Most of the publicity was given to the results of phase II/III study comparing standard paclitaxel-carboplatin (PC) regimen to bevacizumab (monoclonal antibody against the VEGFR) added to PC regimen (PCB). Randomized phase II study suggested improved activity of PCB compared with PC; hemoptysis grade 5 was seen in the PCB arm - central tumor location and squamous cell histology were risk factors. Thus, 878 patients with non-squamous cell histology, without gross hemoptysis and without brain metastases were randomized to receive paclitaxel 200mg/m^2 plus carboplatin AUC 6 or the same combination with addition of bevacizumab 15mg/kg. Six cycles of chemotherapy were applied, and patients in PCB arm continued bevacizumab after this, until progression or unacceptable toxicity. PC vs. PCB: RR 10% vs. 27% (p<0.0001), progression-free survival 4.5 vs. 6.4 mo (p<0.0001), median survival 10.2 vs. 12.5 mo (p=0.0075). Of interest was finding that only men could benefit from adding bevacizumab: for men p=0.003, for women p=0.80. Selected toxicities: grade 4/5 neutropenia 16.4% vs. 24.0%, grade 3/4 thrombosis/embolism 3.0% vs. 3.8% and grade 3/4 hemorrhage 1.0% vs. 4.1%. Eleven TRD were recorded, 2 in PC arm and 9 in PCB arm (5 due to hemoptysis). Investigators from ECOG stated that the addition of bevacizumab to PC in patients with non-squamous cell NSCLC provides statistically and clinically significant survival advantage with tolerable toxicity, and that PCB regimen will be the new ECOG's standard in this patient population (5).

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The enthusiasm regarding this successful combination of one targeted agent with conventional chemotherapy (after a list of unsuccessful trials) could be spread also to the report of Davies et al, where intermittent erlotinib was given in the combination with docetaxel, in phase I, designed to achieve pharmacodynamic separation. They hypothesized that pharmacodynamic separation by intermittent delivery of EGFR-TKI with chemotherapy will increase efficacy. The two schedules of administering erlotinib, with docetaxel 70-75mg/m^2 every 3 wks, were applied: arm A - weekly, day 2, 9, 16 (600-800mg), or arm B - days 2-16 (150-300mg). Among 42 patients, 22 were with advanced NSCLC, the median number of cycles applied was 4. Rash, grade 1/2 was experienced in 88% of patients, febrile neutropenia in 19%. Arm A MTD: doc 70mg/m^2, weekly erlotinib 600mg. Arm B MTD: doc 70mg/m^2, erlotinib 200mg d 2-16. Four partial responses were recorded, 4 minor responses, 5 stabilization. The authors stated that intermittent dosing is feasible and active, and that efficacy of arm B is being examined in a phase II study for second-line chemotherapy (6).

Following the same question - to sequence or to integrate, this year at the ASCO meeting the results of two negative phase III trials have been reported, combined bexarotene (rexinoid that selectively activates RXR receptors which modulate functions associated with differentiation, inhibition of cell growth, apoptosis and metastasis) with platinum-based doublets (7, 8).

Platinum or non-platinum-based doublets for conventional cytotoxic chemotherapy was the topic revisited on ASCO 2005 in two large phase III studies. Kosmidis et al compared paclitaxel-gemcitabine with carboplatin-gemcitabine on 445 evaluable patients and revealed equal activity (OS 10.0 vs. 10.5 mo) with more alopecia, myalgia and neurotoxicity in taxane arm, and more myelotoxicity in platinum arm (9). In the study of Treat et al. standard paclitaxel-carboplatin (PC) was compared with gemcitabine-carboplatin (GC) and gemcitabine-paclitaxel (GP) doublets, on 929 patients. Median survival was 7.6mo vs. 8.4mo vs. 7.9 mo respectively, l-year survival was 31% vs. 33% vs. 33%, respectively. CG regimen resulted in a higher incidence of uncomplicated grade 3/4 myelosupression but was associated with less alopecia and neuro-sensory toxicity. The conclusion was that non-platinum and non-taxane gemcitabine-containing doublets demonstrate similar activity to the standard PC (10).

Erlotinib as a first-line treatment was investigated by Giaccone et al. on 54 patients with advanced NSCLC and achieved response rate of 24.5% (1 CR and 12 PR). Responses were seen in both genders (males: 1CR, 3PR, females: 9PR), in 7 adenocarcinomas and 4 bronchoalveolar carcinomas, all responders were former or never smokers. Toxicity was mild, diarrhea, and rash grade 1/2 experienced in 28 patients each. Bilirubin elevation was noticed in 6 patients, grade 1 in 4 patients, and grade 2 in 2 patients. The conclusion was that erlotinib is active and well tolerated as first-line monotherapy in advanced NSCLC (11).

A single-center, phase II study was performed with the same agent, but for the elderly (median age 76 years), in Boston: on 58 patients. Eight patients were discontinued from study, due to toxicity, with one TRD (pneumonitis). Other toxicities, grade 3/4 were: 5 rash, 2 anorexia, 2 hand-foot syndrome, 2 elevation in PT/PTT, 1 GI bleeding, 1 hemoptysis, 1 diarrhea and 1 glositis. RR was 11% and median survival was 10.5 months, leading into conclusion that erlotinib appears to be relatively well tolerated with encouraging activity (12).

With regard to monotherapy for elderly patients, in this report it should be mentioned that randomized study of Japanese authors: docetaxel 60mg/m^2 was compared to vinorelbine 25mg/m^2 day 1 and day 8, every 3 weeks, on 182 patients, PS 0-2. Median age was 76 years. Myelotoxicity was experienced more in the D arm: grade 3/4 neutropenia 83% vs. 69% (p=0.031). Response rate was 22.7% in the D arm and 9.9% in the V arm, and median survival 13.9 mo vs. 9.9 mo, respectively (p=0.038). QoL was also improved in the D arm, in 2 out of 8 items (appetite and fatigue). The authors concluded that monotherapy of docetaxel provided better overall survival than vinorelbine, and also an improvement of disease related symptoms (13).

The population of PS 2 patients was the subject of the largest trial so far, especially designed to them, and reported on ASCO 2005: paclitaxel poliglumex (XYOTAX) was combined with carboplatin and compared with standard PC regimen. Paclitaxel poliglumex (PPX) is a macromolecular drug conjugate linking paclitaxel to a biodegradable polymer, poly-L-glutamic acid. In present study, PPX was given in dose of 210mg/m^2 plus carboplatin AUC 6 every 3 weeks, compared with standard PC: median survival was 7.8 mo for PPX arm, and 7.9 for PC arm, 1-year survival 31% for each arm. The toxicity profile was as follows: PPX provided a lower incidence of alopecia, delayed time to neuropathy and reduced rate of arthalgia/myalgia; all grades of gastrointestinal symptoms are comparable in incidence between the arms, as well as the incidence of grade 3/4 hematological toxicities, except higher incidence of grade 3/4 thrombocytopenia in PPX arm (14).

In the field of second-line treatment some reports were of interest at the ASCO 2005 meeting: oral topotecan achieved slightly lower activity compared to IV docetaxel, on 829 patients, in randomized phase III study. Topotecan was given 2.3mg/m^2, d1-5, and docetaxel 75mg/m^2 every 3 weeks, and median time-to-progression was 11.3 weeks (T) and 13.1 weeks (D) p=0.0196, and 1-year survival 25.1 vs. 28.7% (15). In SIGN study, gefitinib (250mg/day) was also compared with standard IV docetaxel 75mg/m^2 q 3wks. Preliminary data, after the analysis of 134 patients, in randomized phase II study, show comparable RR: 15.2% G, 12.7% D, as well as disease control rate: 82.6% and 63.6% respectively. Gefitinib was better tolerated (TRD 0% vs. 4%) (16). Novel proteasome inhibitor bortezomib was given alone (1.5mg/m^2 IV on days 1, 4, 8 and 11 q 21 days), in randomized phase II study on 158 patients, or combined (1.3 mg/m^2 on the same days) with standard IV docetaxel 75mg/m^2. Response rate (RECIST) was 10% for single bortezomib and 15.6% for the combination, median time-to-progression 1.5 vs. 4.0 months, and median survival 7.5 vs. 7.8 months (17). Cetuximab was also studied as second-line treatment, on 66 patients in phase II study, and achieved RR of 3.3%, disease control rate 28%, time-to-progression 2.3 mo, median survival 8.1 mo and 1-year 43%. Toxicity profile: rash 77%, grade 3/4 dyspnea 15%, and fatigue 13.6% (18). Of interest are also the results of the IIb phase trial utilizing L-BLP 25 liposome vaccine for the patients with stable or responding disease following any first-line chemotherapy. The authors stated that a clinically significant survival advantage appears likely for patients with stage IIIB, treated with L-BLP 25 (19).

Small-cell lung cancer (SCLC)

Two large, randomized studies investigated the role of topo I inhibitors in the treatment of extensive disease (ED-SCLC). In the first phase III study, 859 patients (PS 0-2) were randomized to receive oral topotecan 1.7mg/m^2 d 1-5 plus cisplatin 60mg/m^2 (TC) or standard etoposide 100mg/m^2 d 1-3 plus cisplatin 80mg/m^2 (EC) every 3 weeks. RR was 63% for TC, 68.9% for EC, and 1-year survival was 31.4% in both arms, median survival 39.3 wks for TC and 40.3 weeks for EC (p=0.47). Grade 4 neutropenia was more pronounced in the EC arm (56.8% vs. 26), but generally both regimens produced comparable activity and tolerability in the therapy-naÔve setting (20). Another study was the confirmation one, after encouraging results of Japanese trial (Noda et al, NEJM 2002) reported improved survival for patients receiving irinotecan-cisplatin. Patients with extensive disease were randomized to receive irinotecan 65mg/m^2 plus cisplatin 30mg/m^2 (IP) on days 1 and 8, or etoposide 120mg/m^2 d 1-3 plus cisplatin 60mg/m^2 (EP) d1. Of 331 randomized patients (2:1), 322 were treated, and the toxicity grade 3/4 profile IP/EP was: neutropenia 36% vs. 86%, febrile neutropenia 4% vs. 10%, anemia 5% vs. 11%, thrombocytopenia 4% vs. 19%, diarrhea 21% vs. 0%. RR IP/EP was 52%/51%, median TTP 4.1/4.6 mo, median survival 9.3/10.2 mo, 1-year survival 35.0/36.1%. The authors concluded that treatment with that modified weekly regimen of IP compared with EP resulted in no significant differences in survival in this patient population. Patients receiving IP had less myelosupression but more diarrhea than EP (21).

Temsirolimus as an inhibitor of mTOR, shown to inhibit tumor cell prolifera-

tion in non-clinical model, was studied as a maintenance therapy, in remission after induction chemotherapy in patients with extensive disease, in a randomized, phase II study, using two dose levels. Following 4-6 cycles of platinum-based doublet with irinotecan or etoposide, 87 patients with CR, PR or SD were randomized to receive 25mg (arm A) or 250mg (arm B), as weekly IV infusion, 4-8 weeks after completing induction therapy. Toxicity was tolerable (grade 3/4: neutropenia 4, thrombopenia 4, hypercholesterolemia 3, allergic reactions 3, urticaria 2) and activity significant: 22.9 mo in higher dose arm vs. 16.5mo in lower dose arm, median TP 6.3 mo vs. 4.7 mo. According to the authors, temsirolimus appears to have significant activity in extensive stage SCLC and should be studied further in this setting (22).
The role of carboplatin-etoposide as a potentially less toxic and an active regimen in treating elderly, or poor performance patients, with extensive stage SCLC was studied in the trial of JCOG. Two-hundred and twenty patients older than 70 and PS 0-2, or younger patients with PS 3 were randomized to receive carboplatin AUC 6, d1 plus etoposide 80mg/m^2 d1-3 (CE) or split doses of cisplatin and etoposide (25mg/m^2 plus 80mg/m^2 d 1-3) (SPE). Most grade 3/4 toxicities, except for thrombocytopenia (55 in CE, 16 in SPE arm), were similar between the arms. There was no significant difference (CE/SPE) for the RR (73/73%), PFS (5.3/4.7mo), OS (10.6/9.8mo), and 1-year survival (41/35%). Thus, CE proved to be equally active and no more toxic regimen, but SPE is still considered to be the standard treatment (23).

REFERENCES

1. Douillard J, et al. J Clin Oncol 2005;23(16s):Abstr7013.

2. Pisters K, et al. J Clin Oncol 2005;23(16s): LBA 7012.

3. Albain KS, et al. J Clin Oncol 2005;23(16s):Abstr 7031.

4. van Meerbeeck JP, et al. J Clin Oncol 2005;23(16s): LBA 7015.

5. Sandler AB, et al. J Clin Oncol 2005;23(16s):LBA 4.

6. Davies AM, et al. J Clin Oncol 2005;23(16s):Abstr. 7038.

7. Blumenschein GR, et al. J Clin Oncol 2005;23(16s):LBA 7001.

8. Jassem J, et al. J Clin Oncol 2005;23(16s):LBA 7024.

9. Kosmidis P, et al. J Clin Oncol 2005;23(16s):Abstr 7000.

10. Treat J, et al. J Clin Oncol 2005;23(16s):LBA 7025.

11. Giaccone G, et al. J Clin Oncol 2005;23(16s):Abstr 7073.

12. Jackman D, et al. J Clin Oncol 2005;23(16s):Abstr 7148.

13. Takeda K, et al. J Clin Oncol 2005;23(16s):Abstr 7009.

14. Langer CJ, et al. J Clin Oncol 2005;23(16s):LBA 7011.

15. Ramlau R, et al. J Clin Oncol 2005;23(16s):Abstr 7017.

16. Cufer T, et al. J Clin Oncol 2005;23(16s):Abstr 7035.

17. Fanucchi MP, et al. J Clin Oncol 2005;23(16s):Abstr 7034.

18. Lilenbaum R, et al. J Clin Oncol 2005;23(16s):Abstr 7036.

19. Murray N, et al. J Clin Oncol 2005;23(16s):Abstr 7037.

20. Eckardt JR, et al. J Clin Oncol 2005;23(16s):Abstr 7003.

21. Hanna NH, et al. J Clin Oncol 2005;23(16s):LBA 7004.

22. Pandya KJ, et al. J Clin Oncol 2005;23(16s):Abstr 7005.

23. Okamoto H, et al. J Clin Oncol 2005;23(16s):LBA 7010.