ASCO 2007: Respiratory oncology in 10 messages

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Summary of Highlights

Early stage non-small cell lung cancer

1. The combination of surgery + adjuvant chemotherapy remains standard for most patients, but induction chemotherapy followed by surgery as an attractive alternative needs more study.
2. Adjuvant biological treatments, such as MAGE-A3 vaccination or erlotinib, reach phase 3 studies.

Locally advanced non-small cell lung cancer

3. The sometimes advocated "Docetaxel consolidation" after chemoradiotherapy for stage III disease proved to be futile and substantially toxic in a phase 3 study.
4. Gefitinib consolidation therapy in this setting resulted in worse survival for unexplained reasons.

Advanced non-small cell lung cancer

5. New enthusiasm for maintenance therapy studies after first-line chemotherapy.
6. No data to support changing the standard of Docetaxel or Pemetrexed in 2nd line treatment of unselected patients.

Biological therapy for non-small cell lung cancer

7. The European phase 3 trial with bevacizumab added to Cisplatin-Gemcitabine resulted in acceptable toxicity in "bevacizumab-eligible" patients and a statistically significant – but clinically minor – difference in progression-free survival. Overall survival data are pending.
8. A Japanese study comparing Gefitinib to Docetaxel in relapse treatment failed to demonstrate non-inferior survival with Gefitinib, despite a better response rate. Results of the INTEREST- and TITAN trials are awaited before considering EGFR-TKIs as 2nd line treatment for unselected patients.

Small cell lung cancer

9. A phase 3 randomised study showed superior control of brain metastases and survival when prophylactic cranial irradiation is offered to patients with extensive SCLC in remission after chemotherapy.

Pleural mesothelioma

10. A randomised phase 3 study with inferior chemotherapy for mesothelioma conducted in the UK did not demonstrate a survival benefit compared to best supportive care.

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Introduction

A total of 423 abstracts in the field of respiratory oncology were accepted at the ASCO 2007 meeting. A total of 208 were accepted for publication only, while 215 were presented, either as poster display (n=148, #7577-7726), at poster discussion sessions (n=49, #7527-7576), or in oral sessions (n=18, #7509-7526). For this report, we mainly concentrated on randomised controlled trial (RCT) data relevant to the practicing clinician, supplemented by a small selection of other abstracts selected for their news value. As this report is only an 'extract from the abstracts', the reader is referred to the full abstract in J Clin Oncol 25, Suppl, pages 387S-440S, for more detailed information by the # sign.

NSCLC – Early stages (I, II, selected IIIA)

In previous years, various studies established the role of adjuvant Cisplatin-based chemotherapy in com-

pletely resected stage II and IIIA NSCLC, while the data remain unclear for stage IB. As compliance with postoperative Cisplatin-based adjuvant chemotherapy is far from optimal, the alternative of preoperative induction chemotherapy has been in the focus of interest for long time. Long-term follow-up data from the US induction chemotherapy for early stage NSCLC were reported (*Figure 1*). Despite the lack of significance (study was stopped prematurely when adjuvant chemotherapy entered clinical routine), a reduction in relapse and death of similar magnitude to the adjuvant data was seen. As a whole, adjuvant chemotherapy remains standard practice, but more studies and individual patient-based meta-analyses are needed to gain more knowledge surrounding the benefits of induction chemotherapy.

Another way to tackle the poor tolerability of postoperative Cisplatin-based adjuvant chemotherapy is to search for better tolerated adjuvant treatments. The final results of a randomised phase 2 study on postoperative immunotherapy targeting the MAGE-A3 antigen (present in 35% of early NSCLC tumours) were reported within this context (*Figure 2*).

NSCLC – Locally advanced stages

Based on non-controlled phase 2 study data from the North-American SWOG investigators, the use of so-called Docetaxel consolidation chemotherapy after concurrent chemoradiotherapy (Cisplatin-Etoposide based) has been advocated – and even practiced – by some. An interesting phase 3 study explored this approach (*Figure 3*) and found no effect whatsoever on outcome and significant toxicity, including a substantial increase in treatment-related hospitalisation and death. This strategy should no longer be pursued.

Moreover, the long-term follow-up data from the randomised SWOG study exploring maintenance therapy with Gefitinib after Cisplatin-Etoposide based chemoradiotherapy followed by Docetaxel – used by that group as a standard in all patients – were reported (*Figure 4*). Gefitinib maintenance therapy did not improve survival, which actually tended to be worse with Gefitinib, for at present incompletely understood reasons. Another still ongoing trial is studying maintenance Erlotinib in patients responding to or in disease stabilisation after 1st line chemotherapy (SATURN trial).

NSCLC – Advanced stages

Modern platinum doublets remain the standard of care for patients with a good performance status, with Docetaxel and Pemetrexed being the two registered 2nd line chemotherapies.

A conceptually challenging abstract compared immediate delivery of a maximum of 6 cycles of Docetaxel after Carboplatin-Gemcitabine 1st line treatment to delayed administration, i.e. at the time of relapse (*Figure 5*). This clearly delayed progression, but the P-value of 0.07 for overall survival was interesting. Maintenance therapy is not ready for clinical practice, but deserves further study.

One large randomised phase 3 study with a non-inferiority design compared the new vinca-alkaloid Vinflunine with a standard Docetaxel arm in patients previously treated with platinum-based chemotherapy (*Figure 6*). Outcome parameters were non-inferior, but some toxicities associated with Vinflunine were severe, so it is unlikely to be considered a viable alternative treatment option in this context.

NSCLC – Biologicals

The results of the AVAiL (AVAstin in Lung cancer) study were eagerly anticipated (*Figure 7*). This study was the European counterpart of the ECOG study that led to registration of Bevacizumab in the US. The European study was statistically designed to compare 2 different dose levels of Bevacizumab (7.5 or 15 mg/kg) with placebo, each Q3W, but not for inter-dose comparison. The study was positive for its statistical endpoint, but the clinical difference in progression-free survival (PFS) was marginal (0.4 to 0.6 months). Overall survival data were not yet reported.

Another interesting abstract was the Phase 3 comparative study of Gefitinib 250 mg/day versus Docetaxel 60 mg/m2 (the standard dose in Japan) in advanced NSCLC patients with 1 or 2 previous lines of chemotherapy (*Figure 8*). The study was set up as a non-inferiority study, with the upper limit of the 95% CI not to exceed 1.25 to conclude non-inferiority of Gefitinib. The study did not meet this endpoint, and survival results favoured Docetaxel, albeit non-significantly. Response and QoL, on the other hand, favoured Gefitinib. This study in an Asian population (where EGFR-TKI therapy has shown better activity) reiterates the as yet unanswered question of whether EGFR-TKI treatment is a valid option for 2nd line treatment in non-selected Western NSCLC patients. Results from the INTEREST (Gefitinib versus Docetaxel) and TITAN (Erlotinib versus Docetaxel or Pemetrexed) studies are eagerly awaited.

SCLC

The main progress in recent years was better integration of CT and RT – including prophylactic cranial irradiation (PCI) – in patients with limited disease SCLC. The chemotherapy itself has not improved substantially over the past 20 years, with Platinum and Etoposide still being the standard of care.

One abstract looked at the role of PCI in patients with extensive disease in remission after chemotherapy (*Figure 9*). The main objective was to reduce the major morbidity associated with the frequent development of brain metastases (BM) in this type of patient. The primary endpoint of reduction of BM was largely met, and somewhat unexpectedly, PCI also improved progression-free and overall survival. This will most probably lead to the use of PCI in extensive disease SCLC in clinical practice.

Mesothelioma

One study in the UK compared ASC with chemotherapy, either MVP (MitomycinC-Vindesine-cis-Platin) or weekly Vinorelbine (*Figure 10*). ASC ("active supportive care") stands for regular specialist visits, use of palliative medication such as corticosteroids, morphine, and palliative radiotherapy where appropriate. No difference in survival nor in symptom control was noted. This contrasts with the findings of the landmark study on Cisplatin-Pemetrexed in this setting, results that were clearly confirmed in abstract #7562 on the large Expanded Access experience with platinum-Pemetrexed. This could be due to the remarkable effectiveness of ASC or due to the selection of inferior chemotherapy. We favour the latter explanation, and feel Cisplatin-Pemetrexed remains the standard of care.

Figure 1: Abstract #7520: Phase 3 RCT on induction chemotherapy before surgery (SWOG).

Patient setting
Early stage NSCLC (stage IB-T3N1).
Randomisation
3 cycles of Carboplatin-Paclitaxel induction chemotherapy -> surgery
versus
Surgery alone.
Outcome
Primary: 5Y overall survival: 50% (combination) vs. 43% (surgery), P=0.19.
Other: median survival 75 vs. 46 months. Survival Hazard Ratio (HR): 0.81. Compliance: 79% had all 3 cycles of induction delivered.
Conclusion
Same benefit in HR as adjuvant chemotherapy, but not significant due to low patient numbers.

Figure 2: Abstract #7554: Phase 2 RCT on postoperative MAGE-A3 immunotherapy.

Patient setting
Completely resected MAGE-A3 positive pathological stage IB and II NSCLC.
Randomisation
Postoperative MAGE-A3 immunotherapy i.m. (5 times Q3W followed by 8 times Q3M)
versus
Placebo same schedule.
Outcome
Primary: Disease-free interval HR 0.73, 95% CI [0.44-1.20], P=0.10.
Other: Survival HR 0.66, 95% CI [0.36-1.20], P=0.09. Very few side-effects.
Conclusion
A reduction in HR comparable to adjuvant chemotherapy, but with minor toxicity. Promising signal in phase 2 RCT strong enough to launch global phase 3 RCT.

Figure 3: Abstract #7512: Phase 3 RCT on Docetaxel consolidation after chemoradiotherapy.

Patient setting
Stage III NSCLC non-progressive after chemoradiotherapy (Cisplatin-Etoposide, 61 Gy).
Randomisation
Docetaxel 75 mg/m^2 Q3W for 3 cycles
versus
Standard follow-up.
Outcome
Primary: Median survival 21.8 (Docetaxel) versus 24.2 (Follow-up) months, P=0.94.
Other: Substantial toxicity: 11% febrile neutropenia, 8% severe pneumonitis, 5% treatment-related death.
Conclusion
No benefit and significant toxicity.

Figure 4: Abstract #7513: Phase 3 RCT on Gefitinib maintenance therapy after chemoradiotherapy.

Patient setting
Stage III NSCLC non-progressive after chemoradiotherapy and Docetaxel consolidation.
Randomisation
Gefitinib 250 mg/day maintenance therapy
versus
Placebo maintenance therapy.
Outcome
Primary: Median survival 23 (Gefitinib) versus 35 (Placebo) months, P=0.013.
Conclusion
Survival with Gefitinib maintenance is worse.

Figure 5: Abstract #7516: Phase 3 RCT on immediate versus delayed Docetaxel after 1st line therapy.

Patient setting
Advanced NSCLC non-progressive after 4 cycles Carboplatin-Gemcitabine.
Randomisation
Immediate Docetaxel 75 mg/m^2 Q3W for 6 cycles
versus
The same at the time of relapse.
Outcome
Primary: Median survival 11.9 (immediate) versus 9.1 (delayed) months, P=0.07.
Other: Median progression-free survival 6.5 versus 2.8 months, P<0.0001. No major increase in toxicity. Similar quality of life.
Conclusion
Data suggest a benefit for the immediate arm.

Figure 6: Abstract #7511: Phase 3 RCT on Vinflunine for 2nd line treatment.

Patient setting
Advanced NSCLC relapsing after one line of chemotherapy.
Randomisation
Vinflunine i.v. 320 mg/m^2 Q3W
versus
Docetaxel 75 mg/m^2 Q3W.
Outcome
Primary: Non-inferior median progression-free survival 2.3 (Vin) versus 2.2 (Doc) months, P=NS.
Other: Differences in toxicity: more grade ¾ fatigue, abdominal pain and injection site reactions with Vinflunine.
Conclusion
No advantage compared to the currently available options.

Figure 7: Abstract #7514: Phase 3 RCT on Bevacizumab added to Cisplatin-Gemcitabine.

Patient setting
Advanced NSCLC 1st line treatment.
Randomisation
Cisplatin-Gemcitabine plus Bevacizumab 7.5 or 15 mg/kg Q3W -> Bevacizumab maintenance
versus
Cisplatin-Gemcitabine plus Placebo, same schedule.
Outcome
Primary: Median progression-free survival 6.5/6.7 (Bevacizumab) versus 6.1 months (Placebo), P=0.03.
Other: Response was higher with bevacizumab (30/34% vs. 20%). Bleeding toxicity was acceptable (7 fatal pulmonary haemorrhages vs. one with Placebo).
Conclusion
Both doses significantly improved progression-free survival, overall survival is to be awaited.

Figure 8: Abstract #7509: Phase 3 RCT on Gefitinib versus Docetaxel in relapsed NSCLC in Japan.

Patient setting
Advanced NSCLC after one or two previous chemotherapies.
Randomisation
Gefitinib 250 mg/day
versus
Docetaxel 60 mg/m^2 Q3W.
Outcome
Primary: HR for Gefitinib 1.12, 95% CI [0.89-1.40], P=0.33.
Other: Response was better with Gefitinib (22% vs. 13%). Quality of life was better with Gefitinib.
Conclusion
Non-inferior survival with Gefitinib could not be proven in Japan.

Figure 9: Abstract #0004: Phase 3 RCT on PCI for extensive disease SCLC.

Patient setting
Extensive disease SCLC with a response after first line Platinum-Etoposide chemotherapy.
Randomisation
Prophylactic Cranial Irradiation (5*4 or 12*2.5 Gy)
versus
Follow-up only.
Outcome
Primary: Reduction of brain metastases at 1 year from 40% to 15%, P<0.0001.
Other: Better overall survival at 1 year, 27% vs. 13%, P=0.003.
Conclusion
PCI should be offered to patients with extensive disease SCLC with response to initial chemo-therapy.

Figure 10: Abstract #7525: Phase 3 RCT on chemotherapy for mesothelioma.

Patient setting
Untreated pleural mesothelioma of any stage.
Randomisation
Chemotherapy with MVP Q3W for 4 cycles or Vinorelbine QW for 12 weeks
versus
Active supportive care only.
Outcome
Primary: Median survival 8.5 (chemotherapy) versus 7.6 (ASC) months, P=0.32.
Other: Similar symptom relief in both arms.
Conclusion
Negative study on older chemotherapy for mesothelioma.

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None reported.