

Report

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Introduction

On 5–7 December 2008, the 3rd Asia Pacific Lung Cancer Conference (APLCC) took place in Hyderabad, India, with more than 720 delegates registered for the event. Owing to the Mumbai bombing, some of the delegates and speakers did not attend, but overall it was a great success for which the organizers, P. Parikh and A. Ranade, are to be congratulated.



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The meeting comprised meet-the-professor sessions, educational lectures, panel discussions, controversies, oral poster presentations, and poster viewings. It covered all aspects of lung cancer and focused on regional differences, specifically for the Asian and Indian population. Participants appreciated that there were plenty of opportunities to interact with both the local and international faculty.

The start of the meeting saw the presentation of the abstract book, the program book, and the second volume of *The Oncology Knowledge Bank* on lung cancer.

This report presents a selection of the educational sessions.

Epidemiology and molecular biology

The first session covered the epidemiology and molecular biology of lung cancer. M. Gottfried discussed the important role of tobacco use in the development of all types of lung cancer. Occupational exposure to asbestos, chromium, arsenic, and domestic radon may also contribute to lung-cancer development, although this is relatively limited in the general population.

The majority of lung cancers today are non-small cell lung cancers (NSCLCs), while 12–20% is of small cell lung cancer (SCLC) histology. In the NSCLC group, adenocarcinoma is more common in never-smokers, while squamous cell carcinoma and other histological subtypes are more frequent in smokers. There is also a biologic difference in response to treatment both to chemotherapy and epidermal growth factor receptor (EGFR)-targeting agents among different histological and genetic subtypes.

The role of screening for lung cancer among different risk groups remains unclear, and most patients present with advanced disease, especially in Asian Pacific countries. Low-dose spiral computer tomography (CT) and cytology have a low yield and new “easier to perform” screening tests should be developed.

Diagnosis and staging

The next topic for discussion was the diagnostic work-up of patients with lung cancer. Cytological and histological diagnosis of the disease remains essential and the role of different staging procedures was presented. The majority of participants agreed that a CT scan of the thorax was necessary and that, if possible, a positron emission tomography (PET) scan should be performed. Magnetic resonance imaging (MRI) of the brain might also be of benefit, especially in patients eligible for surgery for large primary tumors.

A. Bakshi discussed the new staging system for lung cancer that the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) will propose. The 7th edition of the *TNM Classification of Malignant Tumors* is scheduled to be published in 2009. Data from more than 100,000 patients with lung cancer were analyzed and several modifications were suggested for the tumor (T) descriptors and the metastases (M) descriptors, although the current node (N) descriptors remain unchanged. These

recommendations further define homogeneous patient subsets with similar survival rates.

- The changes in patients with NSCLC are: additional cutoffs for tumor size, with tumors > 7 cm moving from T2 to T3; reassigning the category given to additional pulmonary nodules in some locations; reclassifying pleural effusion and pericardial invasion as an M descriptor; and the movement of T2bN0M0 patients from stage IB to stage IIA, T2aN1M0 patients from stage IIB to stage IIA, and T4N0-1M0 patients from stage IIIB to stage IIIA.
- SCLC is usually classified using the limited and extensive definition. The tumor, node, and metastasis (TNM) classification should also be applicable for SCLC, but it has only been reported in small surgical series. Survival seems directly correlated to both the T and N categories. TNM staging is recommended for SCLC, and stratification by stage I–III should be incorporated in clinical trials of early-stage disease.

The conference discussed extensively the role of the PET scan in tuberculosis endemic regions. The PET scan is known to be positive in granulomatous disease such as tuberculosis and sarcoidosis and this may interfere with the specificity of the examination. D. Behera presented a study in patients with a solitary pulmonary nodule (SPN) in an endemic tuberculosis region. Patients with a SPN were evaluated by CT scan and PET/CT scan and the standardized uptake value of the PET/CT scan was correlated with histology. In a small group of patients (n = 16), the PET/CT scan could discriminate malignant from benign SPN with a sensitivity of 100% and a specificity of 75%. Therefore it is essential to differentiate between tuberculosis and malignancy as soon as possible to ensure cure in patients with resectable lung cancer and not to lose time by delaying diagnosis.

Translational research and clinical application

C. Belani discussed the role of EGFR inhibitors in patients with advanced NSCLC. Erlotinib in second- or third-line treatment demonstrated a longer survival compared with a placebo in patients with locally advanced or metastatic NSCLC. It has a response rate of 8–12%, regardless of type or number of prior chemotherapy regimens, and a median survival time of 6.7 to 8.4 months. Gefitinib demonstrated a lack of response (median survival time was 9.8 versus 9.9 months and one-year survival rates were 41% versus 42% for the gefitinib 250 mg/day and placebo groups, respectively) compared with the placebo, except in the patient subgroups of never-smokers (no smoking history) and patients of Asian origin. Analyses looking specifically at these subgroups showed significantly longer survival times in the gefitinib group than in the placebo group for never-smokers (n = 375; median survival time 8.9 versus 6.1 months) and patients of Asian origin (n = 342; median survival time 9.5 versus 5.5 months).

Studies of Japanese and Chinese patients have shown much longer survival times and higher response rates

compared with those observed with other chemotherapy regimens and compared with Western patients given gefitinib. In addition, the phase III Iressa Survival Evaluation in Lung Cancer (ISEL) study showed that a high EGFR gene copy number was a predictor of clinical benefit from gefitinib. Also the presence of activating mutations in exon 19 and in exon 21 was translated in EGFR tyrosine kinase inhibitor (TKI) sensitivity.

While the combination of TKIs such as erlotinib or gefitinib with concomitant chemotherapy in first-line treatment of unselected patients with advanced NSCLC did not produce a survival benefit, there was a longer survival (23 versus 10 months) in those receiving additional erlotinib and those using carboplatin plus paclitaxel alone, respectively, in never-smokers in the Tarceva responses in conjunction with paclitaxel and carboplatin trial (TRIBUTE). The negative survival effects in unselected, untreated patients were confirmed by the large phase III Tarceva Lung Cancer Investigation Trial (TALENT), which added erlotinib to cisplatin plus gemcitabine. The two phase III Iressa NSCLC Trial Assessing Combination Therapy (INTACT) trials similarly found no survival benefit from adding gefitinib, another EGFR TKI, to platinum-based chemotherapy in unselected, untreated patients.

In the Iressa Pan-Asian Study (IPASS), 1217 patients with advanced stage IIIB/IV NSCLC were randomized to gefitinib or carboplatin/paclitaxel as first-line treatment. Patients were of Asian origin, were never or light smokers and had an adenocarcinoma histology. Analysis of EGFR mutations was also performed. In patients with an EGFR mutation, the response rate and progression-free survival (PFS) were better with gefitinib than with chemotherapy. In patients with or without the mutation and treated with chemotherapy, PFS was lower than in patients with the mutation treated with gefitinib, while in patients without the mutation and receiving gefitinib only the PFS was the worst.

There followed a lively discussion on the role of the determination of the EGFR mutation and whether gefitinib should be used as a first-line treatment in the Asian Pacific region. Because of the difficulties in requiring fresh tissue on which to perform the mutation analysis and the lower PFS in patients without the mutation and treated with gefitinib, the conclusion was that at the moment first-line treatment with gefitinib was not standard treatment and that, if one should decide on giving patients gefitinib as a first-line treatment, this should only be done after informed consent and with careful monitoring of the patient.

R. Pirker went on to discuss the importance of monoclonal antibodies (mAb) in NSCLC:

- Bevacizumab, an anti-vascular endothelial growth factor (VEGF) recombinant humanized mAb, was tested as a first-line treatment in combination with chemotherapy in two phase III trials.
 - The Eastern Cooperative Oncology Group (ECOG) conducted a first study (E4599), in which 878 patients with recurrent or advanced non-squamous

NSCLC were assigned to either chemotherapy with paclitaxel and carboplatin alone (n = 444) or paclitaxel and carboplatin plus bevacizumab (15 mg/kg; n = 434). Patients in the bevacizumab arm continued bevacizumab after six cycles until progressive disease or intolerable toxicity. Median survival time was 12.3 months in the group assigned to chemotherapy plus bevacizumab, compared with 10.3 months in the chemotherapy-alone group (hazard ratio [HR] for death 0.79; p = 0.003). The median PFS times in the two groups were 6.2 and 4.5 months, respectively (HR for disease progression 0.66; p < 0.001), with corresponding response rates of 35% and 15% (p < 0.001). In the bevacizumab plus chemotherapy group, the rates of hypertension, proteinuria, bleeding, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash, and headache were significantly higher than in the chemotherapy alone group (p < 0.05) and there were two treatment-related deaths in the chemotherapy group and 15 in the chemotherapy-plus-bevacizumab group. The difference between the groups was significant (p = 0.001).

- The second randomized, placebo-controlled, phase III study, the Avastin in Lung (AVAIL) study, evaluated the addition of bevacizumab to chemotherapy (cisplatin plus gemcitabine) in the treatment of patients with advanced NSCLC. About a thousand patients were randomized to receive cisplatin and gemcitabine every three weeks for up to six cycles plus bevacizumab (continued to progression) at 7.5 mg/kg every three weeks, or 15 mg/kg every three weeks, or a placebo. PFS was significantly longer with bevacizumab: 6.1, 6.7, and 6.5 months, respectively, for chemotherapy alone, chemotherapy plus bevacizumab 7.5 mg/kg, and chemotherapy plus bevacizumab 15 mg/kg (HR 0.75; 95% confidence interval [CI] 0.62–0.90; p = 0.002 for bevacizumab 7.5 mg/kg and HR 0.82; 95%CI 0.68–0.98; p = 0.03 for bevacizumab 15 mg/kg). The response rate and response duration were also significantly higher with bevacizumab. However, there was no difference in overall survival.
- Cetuximab is a monoclonal human-murine chimeric antibody against the EGFR and is the first targeted drug to show a survival benefit when added to chemotherapy in patients with NSCLC.
 - In the FLEX trial, cetuximab was added to chemotherapy and compared with chemotherapy alone in first-line treatment. The trial randomized 1125 patients to cisplatin 80 mg/m² d1 and vinorelbine 25 mg/m² d1, d8 q3w plus cetuximab (400 mg/m² initial dose, then 250 mg/m² a week), or chemotherapy alone. The overall survival significantly improved in the cetuximab arm (median 11.3 versus 10.1 months; HR 0.871; 95%CI 0.762–0.996);

$p = 0.0441$). Results from pre-specified subgroup analyses demonstrated that the addition of cetuximab provides a greater benefit in Caucasians ($n = 946$; HR 0.803; 95%CI 0.694–0.928; $p = 0.003$) across all histological types. The response rate was significantly improved in the cetuximab arm (36.3% versus 29.2%; 95%CI 32.3–40.4 and 25.5–33.2; $p = 0.012$). Treatment was generally well tolerated. The most common grade 3/4 adverse events were neutropenia (52.7% versus 51.4%); febrile neutropenia (21.7% versus 15.5%); anemia (13.9% versus 16.7%); acne-like rash (10.4% versus 0.2%); dyspnea (8.6% versus 9.1%); and fatigue (7.3% versus 6.6%).

Radiotherapy

B. Jeremic examined the role of radiotherapy in the treatment of localized NSCLC. Postoperative radiotherapy (PORT) in patients with early stage NSCLC was discredited based on a 1998 meta-analysis of randomized trials that suggested that PORT was detrimental to survival. However, this meta-analysis was based on studies that used older radiotherapy techniques so that no definite conclusions on the role of modern radiotherapy can be made. Advances in imaging have improved the accuracy of staging, patient selection, and target definition, and modern dosimetry and particle-accelerator technologies have advanced the capacity to deliver radiation to the target with less tissue toxicity.

The role of PORT in specific populations shows that this treatment modality might have a place in the treatment of localized lung cancer:

- The Lung Cancer Study Group (LCSG) trial 773 assessed mediastinal radiotherapy (5000 cGy in 5 to 5.5 weeks) following resection of stage II or stage III squamous cell carcinoma of the lung. A marked reduction in local relapse at the site of first failure (from 41% to 3% of all relapses) was observed for patients randomized to receive PORT. This local control advantage did not translate to a survival benefit.
- A Mayo Clinic study of 224 patients with stage IIIA NSCLC showed a benefit from PORT, and a study from the University of Pennsylvania in 200 patients treated with PORT for pathologic stage II or III NSCLC showed the importance of using moderate radiation doses. Overall survival and local control were favorable and the risk of death from intercurrent disease for patients receiving < 54 Gy was only 2%.
- The SEER database (1988–1995), which includes $> 4,000$ patients with resected T1–3, N1/2 NSCLC, suggested that PORT may benefit the N2 population with improved five-year overall survival (22% versus 16%) and cause-specific survival (30% versus 25%). Patients with four positive nodes, whether N1 or N2, also seemed to benefit from PORT.
- A recent randomized trial of 104 stage I patients from the Università Cattolica del Sacro Cuore with modern radiotherapy techniques (including CT planning with

heterogeneity correction) showed an overall survival benefit for the PORT arm over surgery alone, with five-year survival rates of 67% and 58%, respectively ($p = 0.048$).

There are few trials investigating the benefit of PORT integrated with systemic therapy.

- The concurrent initiation of PORT and adjuvant chemotherapy allows both modalities to be given in a timely manner after surgery. The ECOG 3590 intergroup trial evaluated this approach, comparing PORT only versus PORT plus concurrent etoposide and cisplatin in patients with pathologic stage II or IIIA NSCLC. The PORT schedule was 50.4 Gy in 28 daily fractions, with a boost of 10.8 Gy to regions of extracapsular spread. Toxic side effects were more common in the chemotherapy arm, but treatment-related deaths were $< 2\%$ overall. No differences in survival, in-field relapse, or locoregional relapse were observed between the arms. Death from intercurrent disease at four years was 15.4% for patients who received PORT and 18.4% for patients treated with combined therapy. Although these figures are significantly different from the expected rate of intercurrent disease (based on mortality rates for age- and gender-matched controls derived from US vital statistics and corrected for smoking status), the trial did not have an appropriate (no PORT) control arm.
- The combination of neo-adjuvant chemotherapy and radiation therapy is indicated for superior sulcus tumors based on the Southwest Oncology Group (SWOG) 9416 trial in 110 patients with T3 or T4 and N0 or N1 disease treated with cisplatin and etoposide plus 45 Gy of radiation therapy. By this approach 75% of patients were amenable for complete resection. The median survival time in this group was 94 months, with a complete, or near complete, pathological response in 61% of patients. After surgery, patients received an additional two cycles of the same chemotherapy. Overall, the median survival time for the resected group was 94 months, compared with 33 months for the entire group.
- Patients with stage IIIA, N2 disease are another potential indication for preoperative chemoradiation. This group of patients is very heterogeneous, including those with N2 disease incidentally found at the time of surgery or mediastinoscopy, non-bulky N2 disease found on CT scan and/or PET scan, and bulky N2 disease. Results of clinical trials using neoadjuvant combined chemoradiation therapy in N2 disease are inconclusive.
- With the availability of newer chemotherapy agents and modern radiation techniques, the role of surgery following concurrent chemoradiation has been questioned. The Intergroup 0139 study evaluated definitive chemoradiation versus induction

chemoradiation followed by surgery for stage IIIA N2 NSCLC. PFS was longer with the addition of surgery in this randomized trial (12.8 versus 10.8 months; HR 0.77; $p = 0.017$), but the five-year overall survival rates were similar (27.2% versus 20.3%; HR 0.63; $p = 0.10$). The rate of pathologic complete response was 18% and the rate of nodal clearance (N0 status) was 46%. Subset outcome analysis by type of surgery (lobectomy versus pneumonectomy) and nodal down-staging at surgery (pN0 versus pN1–3) was unplanned and exploratory. Patients undergoing lobectomy versus pneumonectomy were matched by performance status, age, sex, and T stage, but not weight loss or single N2 versus multiple N2 nodal involvement. Independent favorable prognostic factors for overall survival for the entire trial population were absence of weight loss (< 5% versus 5%), female gender, and one N2 nodal station versus two or more N2 nodal stations.

Jeremic concluded that randomized studies should be performed to determine the role of modern radiotherapy in localized NSCLC.

Surgery

The session on surgery addressed the different aspects of surgery in patients with resectable NSCLC. Surgery is considered the treatment of choice for patients with resectable stage I and II (and some patients with stage IIIA) NSCLC.

- In a meta-analysis of randomized controlled trials, four-year survival was superior in patients with stage I–IIIA NSCLC undergoing resection who had complete mediastinal lymph node dissection compared with lymph node sampling (HR 0.78; 95%CI 0.65–0.93).
- There is an increased rate of local recurrence in patients with stage I NSCLC treated with limited resection compared with lobectomy.
- One small study reported a survival advantage among patients with stage IIIA NSCLC treated with chemotherapy followed by surgery compared with chemotherapy followed by radiotherapy. No other trials reported significant improvements in survival after surgery compared with non-surgical treatment.
- In patients undergoing a pneumonectomy survival was lower than in patients undergoing lobectomy.

T. Kohna described the possibilities of video-assisted thoracoscopic surgery in patients with localized disease.

Chemotherapy

Chemotherapy has a definite place in the adjuvant and advanced treatment of patients with NSCLC.

Adjuvant setting

Adjuvant chemotherapy has become the standard of care

for patients with resected stage II and IIIA NSCLC. The role of adjuvant therapy for stage I patients continues to evolve. Several international trials have been reported showing the benefit of adjuvant chemotherapy:

- The International Adjuvant Lung Trial (IALT) showed a statistically significant 4% survival advantage at five years (HR 0.86; $p < 0.03$) with the addition of four cycles of cisplatin-based chemotherapy after complete resection of stage I–III NSCLC. In this trial, 1,867 patients with stages I–III NSCLC were randomized to cisplatin-based chemotherapy versus observation.
- The National Cancer Institute of Canada JBR.10 trial randomized 482 patients with completely resected stage IB–IIB NSCLC to receive four cycles of cisplatin and vinorelbine versus observation. A 15% survival advantage was reported at five years (HR 0.70; $p = 0.012$) with the addition of chemotherapy. There was no benefit for stage IB patients (HR 0.94).
- The Cancer and Leukemia Group B (CALGB) trial 9633 in 344 patients with resected stage IB NSCLC showed a survival advantage for those receiving adjuvant carboplatin and paclitaxel chemotherapy versus observation. This was the only adjuvant trial to use a carboplatin-based regimen. CALGB 9633 was closed early when the first interim analysis demonstrated a 12% survival advantage at four years (HR 0.62). However, a recent update showed an HR for overall survival of 0.80 ($p = 0.10$), with a statistically significant survival advantage at two and three years that was lost by five years. CALGB 9633 failed to show a statistically significant overall survival advantage to carboplatin, but it was a small study and the only trial that exclusively included stage IB patients. The impact that carboplatin had in these results is therefore difficult to evaluate.
- The Adjuvant Navelbine International Trialist Association (ANITA) trial randomized 840 patients with resected NSCLC stages IB–IIIA and found a 9% survival advantage at five years (HR 0.79; $p = 0.013$) with four cycles of adjuvant cisplatin and vinorelbine. No benefit was found for the stage IB patients on subset analysis (HR 1.10; 95%CI 0.76–1.57).
- The Lung Adjuvant Cisplatin Evaluation (LACE), a meta-analysis of these recent trials, found a 5.3% absolute survival advantage at five years (HR 0.89; 95%CI 0.82–0.96; $p = 0.004$) for adjuvant cisplatin therapy. The stage IB subset analysis trended toward benefit (HR 0.92), but failed to reach statistical significance (95%CI 0.78–1.10), while a detriment for chemotherapy was suggested in stage IA patients (HR 1.41; 95%CI 0.96–2.09). In the LACE meta-analysis, the combination of cisplatin plus vinorelbine was found to be superior to other cisplatin combinations.
- A Japanese randomized phase III study of 978 stage I adenocarcinoma patients tested the oral agent uracil-tegafur (UFT), given daily for two years, and demonstrated an HR for survival of 0.71 ($p = 0.04$). The

HR for survival for UFT in a meta-analysis of six trials (95% stage I) was 0.74 ($p = 0.001$). The benefit was limited to those with tumor size of at least 2 cm.

- The Randomized Double-blind Trial in Adjuvant NSCLC with Tarceva (RADIANT) study is evaluating the role of erlotinib in the adjuvant treatment of 975 patients with resected stage IB–IIIA NSCLC. For two years, patients receive daily oral erlotinib therapy at 150 mg/day or a placebo. Results are awaited.

Advanced setting

C. Belani and A. Chang spoke about the different chemotherapeutic aspects of first-line treatment and second-line treatment, respectively, in patients with advanced NSCLC.

First-line treatment

Treatment options for patients with advanced NSCLC should be chosen based on patient performance status. In patients with a good performance status (PS) of 0–1, combination chemotherapy is considered the standard of care. Both platinum-based two-drug regimens and non-platinum combinations have been shown to be efficacious in the first-line treatment of advanced NSCLC:

- A meta-analysis of randomized clinical trials showed the benefits of platinum-based combination chemotherapy over best supportive care as a first-line treatment for patients with advanced NSCLC. The analysis demonstrated that cisplatin-based chemotherapy was associated with a 10% greater one-year survival rate (HR 0.73). This led to the evaluation of several platinum-based combinations for the first-line treatment of advanced NSCLC. In a first generation of randomized clinical trials, single-agent cisplatin was compared with combination treatment with a taxane, gemcitabine, or vinorelbine. The two-drug combinations had a superior efficacy, but at the expense of added toxicity. The different combination regimens were compared in the ECOG 1594 trial, a four-arm randomized phase III study. There was no difference in efficacy and the toxicity profile of cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel, with a reference regimen of cisplatin plus paclitaxel.
- In Japan, the combination of irinotecan with cisplatin was compared with carboplatin plus paclitaxel, cisplatin plus vinorelbine, and cisplatin plus gemcitabine in a four-arm randomized clinical trial. There were no differences and the regimen of cisplatin plus irinotecan is used commonly in Japan for patients with advanced NSCLC.
- Carboplatin-based regimens are easy to administer in the outpatient setting and have favorable non-hematologic toxicity profiles compared with cisplatin-based regimens. Several studies have been conducted to compare carboplatin-based regimens with cisplatin-based combinations in the first-line treatment of

patients with advanced NSCLC. In two meta-analyses of studies comparing cisplatin- and carboplatin-based regimens, cisplatin-regimens that included a newer agent showed a slightly higher response rate and longer survival time. Because systemic chemotherapy is administered with the primary goal of palliation, the debate continues as to whether the marginal superiority of the cisplatin-based regimens justifies their use in routine patient care, given that the associated adverse events may have a negative effect on patient quality of life.

- The use of non-platinum regimens has been widely investigated with a view to improving the therapeutic index of chemotherapy for patients with advanced NSCLC. Randomized trials and a meta-analysis that directly compared platinum-based regimens with non-platinum combinations have demonstrated comparable results, and non-platinum regimens are a reasonable choice for first-line therapy of advanced NSCLC.
- Researchers compared three-drug chemotherapy combinations with standard two-drug regimens to improve treatment outcome. However, there was no difference in efficacy with the addition of a third cytotoxic agent and the toxicity profile was worse.
- Efforts have been made to individualize therapy based on molecular markers in the tumor that predict resistance to specific chemotherapeutic agents:
 - Excision repair cross-complementing 1 (ERCC1) gene over-expression has been linked to resistance to platinum. In a randomized study patients were assigned to treatments based on ERCC1 (mRNA) levels in the tumor tissue at baseline. Patients with low ERCC1 mRNA levels were treated with cisplatin plus docetaxel, whereas those with high levels were treated with gemcitabine plus docetaxel. Response rates with cisplatin plus docetaxel were higher in patients with low ERCC1 expression, although no difference in survival has been observed.
 - Similarly, over-expression of the ribonucleotide reductase M1 (RRM1) gene has been linked to resistance to gemcitabine therapy. A randomized phase II clinical trial demonstrated the feasibility of selecting therapy based on RRM1 expression, and reported high response rates with such a pharmacogenomic treatment selection.

Such novel and individualized strategies will lead to further optimization therapy in the foreseeable future.

- The concomitant administration of chemotherapy and mAb's (e.g. cetuximab and bevacizumab) resulted in a better treatment outcome (cfr. supra). The concomitant administration of chemotherapy and TKIs or other targeted agents did not translate to a survival benefit.
- Although most patients with advanced NSCLC are

treated with four to six cycles of chemotherapy depending on the response, recent data show that maintenance treatment may have a place in the treatment of this patient group:

- Several chemotherapeutic agents have been tested as maintenance treatment but neither taxanes, gemcitabine, or conventional chemotherapeutic agents translated to a survival benefit and also increased toxicity.
- Pemetrexed, a multi-targeted antifolate compound, was compared with a placebo as a maintenance treatment in 663 patients with NSCLC having stable disease or response following four cycles of platinum-based therapy placebo. Pemetrexed had a better efficacy with respect to PFS (4.3 versus 2.6 months; HR 0.502; 95%CI 0.42–0.61; $p < 0.00001$) and tumor response ($p < 0.001$), especially in non-squamous histology (adenocarcinoma). Preliminary overall survival was 13.0 months with pemetrexed and 10.2 months with the placebo (HR 0.798; 95%CI 0.63–1.01; $p = 0.060$), but in a subgroup analysis, overall survival was better in patients with an adenocarcinoma and who were treated with pemetrexed compared with a placebo.

Second-line treatment

The US Food and Drug Administration (FDA) currently approves three agents in the second-line setting: docetaxel, pemetrexed, and erlotinib. The FDA approved these agents based on four phase III trials.

- Docetaxel in second-line therapy showed activity in two phase III trials.
 - The TAX 317 trial initially compared docetaxel at a dose of 100 mg/m² every three weeks with best supportive care (BSC), but the dose was reduced to 75 mg/m² after five treatment-related deaths. There was a longer time to progression, longer median survival, and greater one-year survival rate with docetaxel (75 mg/m²) over BSC.
 - The TAX 320 trial compared docetaxel at 100 mg/m², docetaxel at 75 mg/m², and a control arm of either vinorelbine (30 mg/m²) on days 1, 8, and 15, or ifosfamide (2 mg/m² a day) on days 1–3 every three weeks. While overall survival was not different among the three treatment groups, the one-year survival rate was significantly higher with docetaxel at 75 mg/m² compared with controls.

These trials established docetaxel at a dose of 75 mg/m² every three weeks as the standard therapy in the second-line setting.

- Pemetrexed was compared with docetaxel in a phase III non-inferiority trial and demonstrated similar clinical efficacy. Pemetrexed had a significantly lower rate of hematologic toxicity, including a lower rate of febrile neutropenia and a similar rate of grade 3 or 4 non-hematologic toxicities.

- The National Cancer Institute of Canada BR.21 trial tested second- or third-line erlotinib, comparing it with BSC in 731 patients with advanced NSCLC. Erlotinib produced significantly higher progression-free and overall survival rates and was well tolerated. The principal toxicities were rash and diarrhea. An exploratory univariate analysis demonstrated that the survival benefit with erlotinib was similar across multiple subgroups.

Small cell lung cancer

D. Ettinger examined the topic of SCLC. This histological type represents less than 15% of all lung cancers. The malignant cells have a high propensity for early metastases and only 30–40% of patients present with limited disease (LD) at the time of diagnosis.

- Patients with LD are mostly treated by chemotherapy with thoracic radiotherapy (TRT) and prophylactic cranial irradiation (PCI), although surgery followed by this approach remains an option. In patients with LD the overall response rates are 85–95%, median survival is around 20 months, and two-year disease-free survival is around 20%.
- In patients with extensive disease (ED), the complete response rates are around 20%, median survival is 8–10 months, and almost all patients die within two years. ED patients are treated with chemotherapy and PCI has shown to translate to a survival benefit in patients with adequate response.

Several strategies have been developed to improve these figures:

- An increase in the dose of thoracic radiotherapy has been examined. Doses of 45–50 Gy (administered in daily fractions of 1.8 to 2 Gy) were used because of the radiosensitivity of SCLC. However, although response rates were high, durable local tumor control was poor.
- Intensifying the radiotherapy dose was one of the initial strategies explored in prospective LD-SCLC trials.
 - Turrisi *et al.* randomly assigned 471 LD-SCLC patients to either 45 Gy over five weeks (1.8 Gy a day for 25 fractions) or 45 Gy over three weeks (1.5 Gy bid for 30 fractions) beginning with the first of four cycles of etoposide-cisplatin (EP). The five-year survival rate was 26% with accelerated TRT compared with 16% for conventional TRT at the cost of increased grade 3 or 4 esophagitis.
 - A second trial performed by the North Central Cancer Treatment Group (NCCTG) delayed TRT until the fourth cycle of treatment and delivered the twice-daily TRT with a significant break in treatment (48 Gy in 32 fractions with a 2.5-week break after the initial 24 Gy versus 50.4 Gy in 28 fractions on the control arm). The time course to complete

TRT was essentially the same in both arms, and no survival difference was observed.

- Another strategy for increasing the efficacy of treatment is administering a higher total dose of once-daily TRT or administering concomitant boost therapy where twice-daily treatment is administered only during a part of the treatment course. Three CALGB trials in LD-SCLC used 70 Gy of once-daily TRT, establishing the feasibility of this approach. These trials delayed the initiation of TRT until the third cycle of chemotherapy and used the post-chemotherapy tumor volume for radiotherapy planning. Selective elective nodal irradiation was used to a dose of 44 Gy. The incidence of severe esophagitis seemed to be reduced compared with reports of twice-daily radiotherapy, whereas radiotherapy-related pulmonary toxicity was acceptable.
- The optimal timing of TRT relative to chemotherapy remains controversial.
 - The National Cancer Institute of Canada reported a phase III trial studying TRT (40 Gy) initiated with either the second or sixth cycle of chemotherapy (cyclophosphamide, doxorubicin, and vincristine alternating with EP). This trial showed a survival advantage for early versus late TRT (five-year survival rate of 20% versus 11%, respectively; $p = 0.008$). However, Spiro *et al.* attempted to replicate this trial using the identical inclusion and exclusion criteria and failed to show a benefit for early versus late TRT.
 - The Japanese Clinical Oncology Group (JCOG) reported a trial comparing TRT 45 Gy bid either with the first cycle of chemotherapy (EP) or after four cycles of chemotherapy. Median survival was 27 months in the concurrent arm versus 20 months in the late (or sequential) arm ($p = 0.097$).
 - Several meta-analyses addressing the timing of TRT have been published.
 - Fried *et al.* showed an advantage of early (administered within nine weeks of starting chemotherapy) versus late TRT in terms of survival. This was particularly evident when cisplatin-based chemotherapy regimens and more intensified TRT were used.
 - De Ruyscher *et al.* reported similar findings with regard to survival when TRT was started within 30 days of starting chemotherapy. The survival advantage was more pronounced if the TRT was completed in less than 30 days.
 - The analyses by Spiro *et al.* suggested that the benefit of early TRT is only realized if the delivery of concurrent chemotherapy is not compromised (compared with the delivery of chemotherapy in the delayed TRT group).
- Although not all individual trials are consistent, the weight of the data and the results of the meta-

analyses strongly suggest a modest benefit to early versus delayed TRT. Early is accepted by most to mean TRT delivered during cycles one to three of chemotherapy. It also seems that the benefit of early concurrent chemoradiation may be maximized by more intensified TRT delivered with uncompromised doses of chemotherapy.

- Another strategy for improvement is integrating newer chemotherapeutic agents into the platform of combined chemoradiation. In general terms, the addition of or substitution of a new chemotherapeutic agent such as paclitaxel, irinotecan, topotecan, and ifosfamide to the standard EP regimen has been tested. Although response rates are high in many of the trials, the median survival times and two-year survival rates are not impressive when compared with the phase III results. Only the JCOG Trial 0202 is comparing three cycles of EP with three cycles of irinotecan/cisplatin after an initial cycle of EP with 45 Gy of twice-daily TRT based on the positive results of cisplatin/irinotecan compared with EP in ED-SCLC, which could not be confirmed in a North American population.
- Second-line treatment in patients with SCLC depends on the sensitivity of the disease (sensitive: relapse more than three months after treatment; refractory: no response or relapse less than three months after treatment). Topotecan has shown activity in patients with sensitive disease, while its activity is limited in patients with refractory disease. Amrubicin, an anthracycline also showed activity in sensitive and refractory disease.

Special situations

D. Raghunadharao discussed malignant pleural mesothelioma (MPM), which is an uncommon neoplasm arising from the mesothelial cells lining the pleura. Rarely, pleural mesothelioma is localized, benign, and readily resectable for cure. It is linked to both occupational and incidental asbestos exposure and is concentrated in areas where people are exposed to asbestos (e.g. shipbuilding and asbestos factories).

Of the two basic types of asbestos, the larger amphibole fibers are the most carcinogenic. Their greater bio-persistence and higher iron content catalyze the production of reactive oxygen radicals.

The initial clinical presentation for most patients with MPM is progressive dyspnea and/or steady chest-wall pain. There may also be a dry cough, weight loss, fever, fatigue, or night sweats. The disease is more commonly found unilaterally (95%) located in the right chest (60%), and it occurs predominantly in men, usually presenting in the sixth through eighth decades. The symptoms of MPM may be insidious and non-specific such that the time from initial presentation until diagnosis is often three to six months.

Diagnosis is made by pleural fluid cytology, which may yield a definitive diagnosis of MPM in 20–33% of patients. A blind core needle biopsy of the pleura modestly improves this

yield. A CT-guided core needle biopsy of one of the pleural masses is more sensitive (87%) in making a diagnosis. In addition to standard histology, special immuno-histochemical stains of the biopsy tissue may be necessary to make a definitive diagnosis of MPM because of its histomorphologic similarities to adenocarcinoma.

MPM does not have one widely accepted treatment since none reliably results in cure. Moreover, there is a striking lack of randomized, clinical trials comparing treatment regimens in this disease, due in part to its relatively low incidence.

- Complete surgical resection is theoretically the most effective treatment. However, with the usual diffuse spread of MPM throughout the hemi-thorax, complete resection of this neoplasm with histological negative margins is rarely achieved, so surgery has a limited role in this malignancy.
- Radiotherapy has also limited indications in MPM since it is difficult to deliver adequate doses (> 60 Gy) to the entire neoplasm.
- Different chemotherapeutic agents have shown activity in MPM:
 - In a randomized trial reported by Muers *et al.* in 409 patients with MPM treated with active supportive care (ASC; treatment with steroids, analgesic drugs, bronchodilators, palliative radiotherapy), ASC plus MVP (four cycles of mitomycin 6 mg/m², vinblastine 6 mg/m², and cisplatin 50 mg/m² every three weeks), or ASC plus vinorelbine (one injection of vinorelbine 30 mg/m² every week for 12 weeks), there was no survival benefit for ASC plus chemotherapy (HR 0.89; 95%CI 0.72-1.10; p = 0.29) with a median survival time of 7.6 months in the ASC alone group and 8.5 months in the ASC plus chemotherapy group.
 - Based on a phase III trial comparing cisplatin with cisplatin plus pemetrexed, this combination is considered to be the standard first-line treatment because of a significant survival advantage (9.3 versus 12.1 months) for the combination.
 - When pemetrexed plus BSC was compared with BSC alone in a phase III study there was no difference in median overall survival time (8.4 versus 9.7 months; p = 0.74). Partial response was achieved in 18.7% and 1.7% of patients in the pemetrexed plus BSC and the BSC arms, respectively (p < 0.0001), and a disease control rate (partial response plus stable disease) was achieved in 59.3% and 19.2% of patients in the pemetrexed plus BSC and the BSC arms, respectively (p < 0.0001). Chemotherapy was well tolerated, with expected modest (4–7%) grade 3 and 4 hematologic toxicities.

D. Schrijvers discussed the topic of elderly patients with lung cancer. This is an important issue since the majority of patients with lung cancer are aged above 65 years and the changing demographics will result in an even higher number

of senior people who will develop lung cancer and be in need of subsequent cancer treatment and care. When dealing with these patients several factors such as life expectancy, co-morbidity, and geriatric syndromes should be taken into account. Senior lung cancer patients may be fit, vulnerable, or frail. For fit elderly patients there are some evidence-based data by sub-group analyses of clinical trials, but information on vulnerable and frail elderly patients is almost lacking, apart from some studies in patients with advanced lung cancer.

S. Dattatreya discussed the group of patients with a bad performance status (PS). Data on this group of patients are also scarce since in most trials they are excluded. Patients with a PS of 2 have a poorer prognosis but can sometimes receive single-agent treatment. A reduction in PS as a result of an aggressive tumor warrants standard combination chemotherapy to achieve the best results.

Clinical trials in lung cancer

C. Desai focused on endpoints in clinical trials. The endpoint depends on the aim of the study and in phase I trials this is toxicity, in phase II trials activity, and in phase III trials the comparison with standard treatment or care.

In this last type of trial, endpoints such as overall survival or quality of life should be addressed. However, the long duration of such trials led to the definition of surrogate endpoints such as progression- or disease-free survival or response rate. Desai also discussed the problems of endpoint trials with targeted agents.

Conclusion

This 3rd Asia Pacific Lung Cancer Conference provided an in-depth overview of all aspects of lung cancer and the lively discussions with the delegates were an added bonus.

The 4th APLCC will take place in 2010 in Korea.

For all presentations at the 3rd Asia Pacific Lung Cancer Conference please refer to the October supplement issue of the Indian Journal of Cancer.

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