CHAPTER

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Recent Advances in the Management of Lung Cancer

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Introduction

Lung cancer constitutes the main cause of cancer deaths for both men and women worldwide. In India the annual crude incidence rate of lung cancer is 0.1 per million of urban population. It occupies the first place among all cancers in the males in Mumbai, Delhi and Bhopal cancer registries.[1] Close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. Only about 15% of all patients with NSCLC survive this disease longer than five years after diagnosis. Approximately 85% of all cases of lung cancer are of the non–small-cell type (NSCLC).[2] 10-15% is small cell type (SCLC). Relapse most often occurs at distant sites, suggesting that lung cancer is commonly a systemic disease at diagnosis.

Staging

Appropriate management of lung cancer depends on precise disease staging and accurate response assessment. International association for study of lung cancer (IASLC) has proposed changes in the staging of NSCLC and SCLC for the fourth coming revision of the AJCC/UICC staging based on the analysis of more than 100,000 patient data base. The proposed changes in the staging are given below.

The recommendations of the T descriptors sub-committee were:

- T1 as
  - T1a (≤ 2 cm) or
  - T1b (> 2 cm to ≤ 3 cm); and
- T2 as
  - T2a (> 3 to ≤ 5 cm or T2 by other factor and ≤ 5 cm) or
  - T2b (> 5 to ≤ 7 cm).
- Reclassify T2 tumours > 7 cm as T3.
- Reclassify T4 tumours by additional nodule/s in the lung (primary lobe) as T3.
- Reclassify M1 by additional nodule/s in the ipsilateral lung (different lobe) as T4.
- Reclassify pleural dissemination (malignant pleural or pericardial effusions, pleural nodules) as M1.

The recommendations of the M descriptors sub-committee were:

- Reclassify pleural dissemination (malignant pleural effusions, pleural nodules) from T4 to M1a.
- Subclassify M1 by additional nodules in the contralateral lung as M1a.

Table 1 : 2003–2006 adjuvant trials and meta-analyses

Trial	Stage	*n*	Chemotherapy	Hazard ratio	*p*-value
IALT[5]	I–III	1,867	Cis/vinca or etoposide	0.86	<.03
BR.10[6]	IB–II	482	Cis/vinorelbine	0.70	.012
ANITA[8]	I–IIIA	840	Cis/vinorelbine	0.79	.013
CALGB 9633[9]	IB	344	Carbo/paclitaxel	0.8	.10
UFT meta-analysis[21]	95% stage I	2,003	UFT	0.74	.001
LACE meta-analysis[10]	I–III	4,584	Platinum doublet	0.89	.0004

Table 2 : Summary of Recommendations for Adjuvant Chemotherapy

Stage	Summary of Recommendations for Adjuvant Cisplatin- Based Chemotherapy
IA	Adjuvant chemotherapy is not recommended
IB	Adjuvant cisplatin-based chemotherapy is not recommended for routine use
IIA	Adjuvant cisplatin-based chemotherapy is recommended.
IIB	Adjuvant cisplatin-based chemotherapy is recommended
IIIA	Adjuvant cisplatin-based chemotherapy is recommended.
General	The use of adjuvant chemotherapy regimens that include alkylating agents is not recommended as these agents have been found to be detrimental to survival.

Abbreviations: ANITA, Adjuvant Navelbine International Trialist Association; CALGB, Cancer and Leukemia Group B; Carbo, carboplatin; Cis, cisplatin; IALT, International Adjuvant Lung Trial; JBR.10, National Cancer Institute of Canada JBR.10 trial; LACE, Lung Adjuvant Cisplatin Evaluation; UFT, uracil-tegafur.

- Subclassify M1 by distant metastases (outside the lung/pleura) as M1b.

New imaging technics

Common imaging modalities used for staging lung cancer patients include chest radiography, CT, magnetic resonance imaging, (FDG) PET and fused modality imaging (PET-CT). FDG-PET as a single imaging modality has shown to be superior to conventional imaging in direct comparisons with respect to differentiate between benign and malignant pulmonary nodules, mediastinal lymph node metastases and distant metastatic disease (with the noteworthy exception of brain metastases). One drawback of FDG-PET is that it still lacks absolute specificity for differentiating benign (e.g. inflammation) from malignant disease.[3-5]

Treatment

For many years, surgery alone has been the standard treatment for patients with stage I-IIIA NSCLC. Even with complete resection, 5-year survival rates are disappointing and range from 67% for T1N0 (IA) disease to 23% for patients with T1-3N2 (IIIA)[6]. Adjuvant chemotherapy for resected early-stage NSCLC was still a research question until a few years ago, but has now become the standard of care for patients with resected stage II and IIIA disease. The role of adjuvant therapy for stage I patients, though, continues to evolve. Prior to 2003, no large randomized studies had conclusively demonstrated the benefit of adjuvant chemotherapy after resection of NSCLC, despite the results of a 1995 meta-analysis demonstrating a nonsignificant 5% survival advantage at 5 years with the addition of cisplatin based chemotherapy.[7]

The first several phase III studies reported after the meta-analysis failed to show a significant benefit with adjuvant chemotherapy. These included the Eastern Cooperative Oncology Group (ECOG) 3590[8], Intergroup 0115 trial, the Big Lung Trial (BLT)[9] and the Adjuvant Lung Project Italy (ALPI) trial[10] (Table 1).

However newer trials since 2003 started showing showing a survival benefit with the addition of adjuvant chemotherapy (Table 2).

Role of Adjuvant Chemotherapy in stage I-IIIA completely resected NSCLC

Chemotherapeutic agents

The use of adjuvant chemotherapy involving alkylating agents is not recommended because it has been found to shorten survival.[11] Platinum is the mainstay of treatment for patients with lung cancer. Usually doublets are used i.e. combination of platinum with other drugs like etoposide, gemcitabine, taxanes and vinorelbine. NCIC-CTG JBR.10, IALT, & ANITA trials and LACE metaanalysis achieved a statistically and clinically significant survival benefit for adjuvant chemotherapy using vinorelbine combined with cisplatin.[12-13] Major drawback in the use of this regimen is the weekly administration schedule. A recent randomized trial showed that, in advanced NSCLC, a 3-weekly cycle of vinorelbine on days 1 and 8 and cisplatin on day 1 has better tolerance and similar efficacy to the regimen administered in the adjuvant setting described above.[14] Of the platinums (cisplatin and carboplatin), cisplatin-based regimen remain the standard in the setting of adjuvant chemotherapy for resected early stage NSCLC, with carboplatin as a substitute only in patients with clear contraindications to cisplatin.[15]

Adjuvant chemotherapy in the elderly

The Elderly Vinorelbine Study (ELVIS) was a landmark trial in advanced NSCLC, which in a randomized fashion demonstrated that the elderly enjoy not only a survival benefit from chemotherapy, but an improvement in quality of life as well.[16] A retrospective analysis of the JBR.[10] trial concluded that patients over the age of 65 years with a good performance status benefit from adjuvant chemotherapy, but those over 75 years of age require further study.[17]

Treatment of Unresectable Stage IIIA/ IIIB Lung Cancer

For patients with clinical stage IIIB unresectable NSCLC, combined-modality treatment (chemotherapy with radiation) is the standard of care.[18-20] Two treatment strategies, induction chemotherapy and concurrent chemoradiotherapy, have demonstrated favorable effects on survival and are superior to radiotherapy alone. Several groups of investigators have directly compared the two treatment strategies in phase III clinical trials. The first published data came from Japanese investigators, who compared the use of sequential chemoradiotherapy with that of concurrent chemoradiotherapy. The median survival time was 16 months vs 13 months for the concurrent administration.[21] Similar results were observed in the Radiation Therapy Oncology Group study 9410, which showed superior 5-year survival rates with concurrent therapy compared to sequential therapy with CDDP and vinblastine.[22]

Treatment of Metastatic Lung Cancer

It has been proved in many randomized trials that systemic chemotherapy is superior to best supportive care in patients with locally advanced and metastatic lung cancer.[23] Platinum-based chemotherapy has been widely accepted as the standard of care compared to non-platinum based therapy.[24-25] Cisplatin-based chemotherapy resulted in increased median survival time (1.5 months) and reduced the risk of death by 27%.[24] In the first line setting platinums have been combined with agents such as Paclitaxel, Docetaxel, Gemcitabine and Vinorelbine have been proved to be equally effective.

Platinum-Based or Non-Platinum-Based Regimens?

Due to the toxicities associated with platinum based chemotherapy, non-platinum-based regimens, in particular taxane (paclitaxel/docetaxel) -based regimens, have been the focus of intense research.

A recent randomized study[26] of 413 patients compared a platinum-based regimen, CISPLATIN+VINORELBINE, with a non-

platinum-based regimen, Docetaxel+ Gemcitabine. The median survival time was similar between the two studies (9.7 month v/s 9.0 months), but toxicity was higher in the Cisplatin + Vinorelbine arm. The results of this study were later confirmed by a French trial[27] of 311 patients randomized to receive Cisplatin + Vinorelbine or Docetaxel+ Gemcitabine chemotherapy regimens.

Taxane based chemotherapy in combination with Gemcitabine (Paclitaxel + Gemcitabine therapy) has also proven to be equally effective when compared to Carboplatin + Gemcitabine or Paclitaxel + Carboplatin therapy.[28-29]

Three-drug cytotoxic combination regimens have been tried in the management of advanced NSCLC; however it was found to be more toxic and is not recommended.

Targeted Therapy

Though it is clear that chemotherapy is an appropriate treatment for many patients with lung cancer, the use of traditional chemotherapeutic agents has reached a therapeutic plateau. Increased understanding of cancer biology has revealed numerous potential therapeutic strategies, including targeting the epidermal growth factor receptor (EGFR) protein kinase C, rexinoid receptors, and the angiogenesis pathways. Alteration of the major cell signaling and regulatory pathways either by overexpression or gene mutation is a frequent event in lung cancer. These include alterations in receptor tyrosine kinases (RTKs) such as the EGFR, alterations in angiogenesis pathways, apoptosis, proteosome regulation, and cell cycle control, among others.[30]

EGFR Inhibitors

The EGFR is over expressed in 40-80% of patients with NSCLC and is associated with poor prognosis.[31] Agents targeting the EGFR that have been evaluated for use in NSCLC include the small molecule receptor tyrosine kinase inhibitors erlotinib and gefitinib, as well as cetuximab and panitumumab, monoclonal antibodies specific to the EGFR. In the United States, erlotinib is the only EGFR-targeted agent approved by the FDA for use in NSCLC.[32] Erlotinib is indicated for the treatment of patients with locally advanced or metastatic disease after failure of at least 1 prior chemotherapy regimen[33]. Erlotinib extended median survival by 2 months compared with placebo, and 6-month progression-free survival was 25% of patients who received erlotinib compared with 10% of those who received placebo. The objective response rate for erlotinib was 8.2%, and responding patients had a median response duration of 7.9 months. Certain subsets of patients, including Asians, women, never smokers, and patients with adenocarcinoma histologies, were most likely to respond to erlotinib. Despite producing survival benefits in second-line and third-line treatment settings, frontline erlotinib in combination with standard chemotherapy did not improve survival compared with chemotherapy alone.[34]

Gefitinib, which is similar to erlotinib, was the first EGFR targeted agent to be approved for use in patients with previously treated advanced NSCLC. Currently, only patients who benefited previously from gefitinib are able to receive prescriptions for this agent in USA. However it is being widely used outside United States. However, further analysis demonstrated that subgroups of patients may benefit from EGFR therapy. The presence of EGFR mutations have been shown to correlate with clinical features associated with response to gefitinib response, including adenocarcinoma histology, absence of smoking history, female sex, and Asian race.[35]

The monoclonal antibody cetuximab has demonstrated promising antitumor activity in both first- and second-line treatment of NSCLC. In the first-line setting, cetuximab has been investigated in combination with cisplatin/vinorelbine, paclitaxel/carboplatin, and gemcitabine/carboplatin in patients with stage IIIB/IV EGFR-expressing NSCLC.[36] Panitumumab, a humanized EFGR-targeted monoclonal antibody was recently approved for use in metastatic colorectal cancer

and has also demonstrated an acceptable safety profile combined with carboplatin/paclitaxel in patients with NSCLC.[37]

VEGF Inhibitors

Angiogenesis, which involves formation of new blood vessels, is critical to tumor growth and metastasis. As a result, antiangiogenic therapies, such as bevacizumab, are being actively investigated in a variety of cancers.[38] Bevacizumab, a recombinant humanized antibody directed against the VEGF, was the first agent in its class to receive approval for the treatment of patients with cancer. The introduction of bevacizumab has extended survival in the first-line setting when added to carboplatin/paclitaxel, representing the first improvement in survival for NSCLC since platinum-based doublet chemotherapy was introduced 20 years ago.[39] On the basis of the Eastern Cooperative Oncology Group (ECOG) 4599 trial findings the FDA recently approved bevacizumab for first-line treatment of NSCLC in combination with carboplatin and paclitaxel.[40]

Multitargeted Kinase Inhibitors

Multitargeted receptor tyrosine kinase inhibitors of angiogenic signaling are also being evaluated in NSCLC. Vandetanib, targets both the EGFR and VEGFR, Sunitinib principally a VEGF inhibitor but also inhibits the platelet-derived growth factor receptor and other tyrosine kinases & Sorafenib, which inhibits VEGF and platelet-derived growth factor receptor, but also inhibits the growth signaling molecule Raf are the agents in various stages of development.[41-43]

Vaccines

At least three "immunologically based" therapeutics are being investigated in large studies in NSCLC. BL25, a Muc-1 vaccine (Stimuvax) is being tested in stage III unresectable patients in a phase III trial. Recombinant Mage-3 has been investigated in the adjuvant setting in a large phase II randomized study and is proceeding into phase III. Two phase III studies of a Toll-9 receptor agonist have recently been completed in advanced NSCLC and results are awaited.

Molecular profiling

Recent studies have also indicated the ability to prospectively identify patients who are most likely to benefit from adjuvant therapy. A retrospective analysis of a subset of patients from the IALT trial indicates that IHC staining for ERCC1 may help predict those patients most likely to benefit from adjuvant cisplatin-based therapy.[44] ERCC1 is a nucleoside excision repair enzyme involved with the repair of cisplatin-induced DNA adducts. In that analysis, those patients with ERCC1-positive tumors were far less likely to benefit than those with lower levels of this DNA repair enzyme. This is an important step toward identifying the group of patients most likely to benefit from adjuvant cisplatin-based therapy. in the current situation, in which the overall survival benefit from adjuvant therapy is on the order of 5%–10%, and the treatment includes 3 months of relatively toxic chemotherapy, the ability to identify those most likely to benefit is crucial. How best to help those who may be less likely to benefit from cisplatin-based therapy needs further exploration.

EGFR Gene Mutations and Response to EGFR-TK Inhibitors

The observation that certain subgroups of patients, mainly female patients, never-smokers, patients with adenocarcinoma histology, and patients of Asian origin have a higher response rate and clinical benefit with gefitinib and erlotinib therapy prompted research to elucidate the molecular mechanism responsible for this increased response. Three different research groups have presented studies showing a positive relationship between the presence of activating mutations in the EGFR TK domain and a clinical response to gefitinib.[45-47] The most common mutations were in-frame deletions that resulted in the insertion of a serine residue in three mutations (del E746-A750, delL747-T751insS, and delL747- P753insS) on exon 19. Other mutations

consisted of an amino acid substitution within exon 21 (leucine to arginine [L858R] and leucine to glutamine [L861Q]). EGFR mutations (L858R and delL747-P753insS) had increased TK activity compared with wild-type receptors and were more sensitive to inhibition by gefitinib.

Small cell lung cancer

Recent epidemiological data suggest that the incidence of small-cell lung cancer is falling and that the proportion of lung cancer patients with small-cell histology is now ~ 13% (compared with 20–25% previously). Characterisation of patients with SCLC into limited-stage disease (LD) and extensive-stage disease (ED) as defined by the Veterans Administration Lung Study Group (VALG) has been the basis of treatment choice for a number of years. This system is generally accepted in clinical practice; however, it does not accurately segregate patients into homogenous prognostic groups and the appropriate classification of selected sites remains controversial. As a result, the consensus report of the International Association of Lung Cancer (IASLC) revised the VALG classification, in accordance with the tumor, node, metastasis (TNM) system. In the IASLC system, LD is defined essentially as stages I–IIIB, and ED is limited to patients with distant metastasis. Treatment with cisplatin plus etoposide with early, concurrent radiotherapy is the standard of care for patients with limited-stage disease (LD) suitable for this approach. A 5-year survival rate of 25% has been reported for concurrent hyperfractionated radiotherapy. Patients unsuitable for concurrent chemo-radiotherapy are usually treated with a sequential approach – i.e. Initial chemotherapy followed by radiation. Patients with LD who achieves complete response should be offered prophylactic cranial irradiation (PCI). Patients with extensive-stage disease but few other adverse prognostic factors should be treated with a platinum compound plus etoposide. Patients with relapsed disease have a poor prognosis, but there is evidence of a survival benefit for salvage chemotherapy in those fit for treatment. The choice of treatment will depend on a number of factors, including the disease-free interval. Topotecan is the only drug licensed in this indication, but myelosuppression is considerable.[48]

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