Lung Cancer

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Summary: Lung cancer is the leading cause of cancer-related mortality. Since tobacco smoking is the cause in vast majority of cases, the incidence of lung cancer is expected to rise in those countries with high or rising incidence of tobacco smoking. Even though populations at risk of developing lung cancer are easily identified, mass screening for lung cancer is not supported by currently available evidence. In case of non-small cell lung cancer, a cure may be possible with surgical resection followed by post-operative chemotherapy in those diagnosed at an early stage. A small minority of patients who present with locally advanced disease may also benefit from pre-operative chemotherapy and/or radiation therapy to down stage the tumor to render is potentially operable. In a vast majority of patients, however, lung cancer presents at an advanced stage and a cure is not possible with currently available therapeutic strategies. Similarly, small cell lung cancer confined to one hemi-thorax may be curable with a combination of chemotherapy and thoracic irradiation followed by prophylactic cranial irradiation, if complete remission is achieved at the primary site. Small cell lung cancer that is spread beyond the confines of one hemi-thorax is, however, considered incurable. In this era of molecular targeted therapies, new agents are constantly undergoing pre-clinical and clinical testing with the aim of targeting the molecular pathways thought be involved in etiology and pathogenesis of lung cancer.

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The World Health Organization reported 6 million cancers worldwide in Year 2000. Lung cancer accounted for one million, one sixth of these, representing the most common cancer globally.[1] In the United States, one of the countries where accurate and consistent statistics are available, there will be an estimated 186 550 new lung cancers in Year 2004 with estimated 165 130 deaths.[2] Lung cancer accounts for 13% of all cancers in males and 12% of all cancers in females in the US. However, it is responsible for 32% and 25% of all cancer-related deaths in males and females, respectively, representing the largest single cause of smoking related mortality.[2] Despite major financial and research efforts of the past two decades, the five-year survival for lung cancer has remained constant at a dismal 14% in the Western world.[3] Only those presenting at an early stage appear to have a chance at cure.

The age-specific incidence rate for lung cancer in Saudi Arabia is 25 per 100 000 population (Figure 1). Lung cancer is the 4th most common cancer among males and 7th among females.[4] Considering the incidence of smoking in males, this number appears small and may represent a lag time between the increased incidence of smoking and the rise in the incidence of lung cancer. It is thus expected that in coming years lung cancer will represent a major public health problem in the Kingdom of Saudi Arabia. Concerted efforts are thus needed not only to educate the general public regarding the hazards of smoking and early symptoms and signs of the disease, but also health care providers to not only educate the public but also to diligently diagnose lung cancer at its early and potentially curable stage. This article will thus attempt to briefly analyze etiology, prevention, and screening strategies as well as new advances in management.

Etiology, Pathogenesis & Pathology

Smoking is the major etiologic factor for lung cancer, with approximately 90% to 95% of new lung cancers resulting from active smoking.[5,6] Among non-smokers a quarter of lung cancers

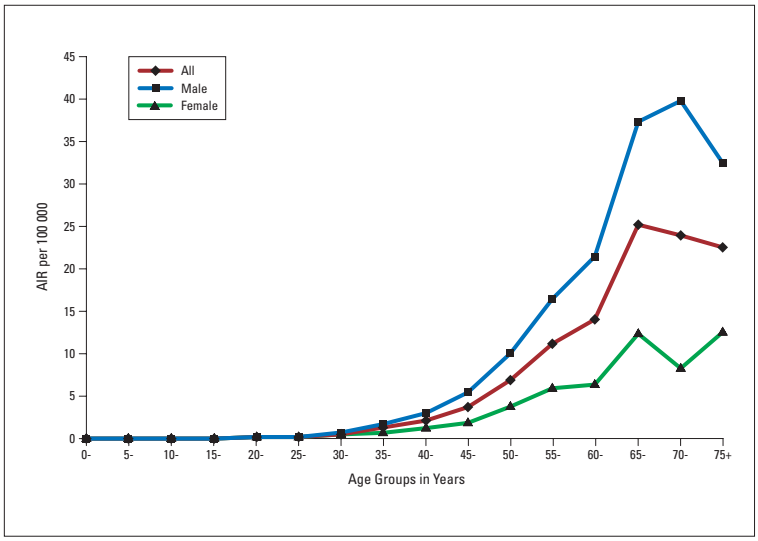

Figure 1. Average age-specific incidence rate (AIR) for lung cancer, Saudi Arabia, 1994-2000.

are caused by second hand smoke (passive smoking).[7-9] Since only 10% of the smokers develop lung cancer, other factors seem to play a part.[10] These might include the genetic make-up of an individual as well as other environmental insults such as asbestos exposure. Other etiologic factors include exposure to asbestos[11] or other environmental agents like silica,[12] beryllium,[13] nickel,[14] diesel exhaust,[15] or radon,[11] although the data regarding these, except for asbestos exposure are conflicting. Lung cancer starts with premalignant changes in the epithelium and develops from squamous metaplasia through carcinoma in situ to frank invasive cancer.[16] Environmental factors are thought to be critical in pathogenesis, although they may not be the sole cause.

The World Health Organization divides lung malignancies into several different sub-types but for clinicians it may be divided into two broad categories, i.e. small cell and non-small cell lung cancers, the latter encompassing adenocarcinoma, squamous cell, large cell, and bronchoalveolar carcinomas.

Prevention and Screening

Lung cancer is one of the few cancers with a well-defined etiology—inhalation of tobacco smoke. In addition to first hand smoke, the United States Environmental Protection Agency has also identified passive (second hand) tobacco inhalation to be a carcinogen. At least 24 studies have identified second hand smoke as a risk factor for development of lung cancer, with a relative risk as high as 2-fold in some studies.[7-9] Clearly, cigarette smoking is the most prevalent environmental carcinogen and concerted efforts are required by governments as well as health care providers to support smoking cessation and prevention programs.

Only 10% of all smokers develop lung cancer. Therefore, other factors play a part in the development of lung cancer in addition to tobacco smoke. An individual's genetic susceptibility to the carcinogens present in tobacco smoke may be one such factor.[17] Investigators have identified several enzymatic pathways that may be involved in activation, degradation of carcinogens, and subsequent DNA repair.[18] Members of cytochrome P450,[19-22] glutathione S-transferase,[23-25] epoxide hydrolase,[26] and N-acetyltransferase[25,27,28] are involved in activation and degradation of certain carcinogens found in tobacco smoke. Genes encoding these enzymes may display deletions, mutations, or polymorphisms, thereby affecting the enzyme's activity.

Certain dietary components have also been linked to an increased risk of lung cancer.[29,30] The carotenoids were the first such group identified to have an inverse correlation with lung cancer risk.[31] Several epidemiologic studies have suggested that individuals with diets low in beta-carotene have a higher risk of developing lung cancer.[30,32,33] Other dietary micronutrients like flavonoids[34] and isothiocyanates[35,36] have also been suggested to have inverse correlation with lung cancer risk.

Chemoprevention is an area of intense investigation. Research to date has focused on two separate classes of agents, i.e. dietary micronutrients or their synthetic analogues, and synthetic agents such as NSAIDs.[37] Retinoids have been extensively studied in this regard. One of the first studies to report positive results showed a statistically significant decrease in the incidence of second tobacco-related malignancies (head and neck, lung, esophagus) in those diagnosed with squamous cell carcinoma of head and neck and treated with cis-retinoic acid.[38] A US intergroup trial studied 13-cis retinoic acid in patients with resected stage I lung cancer and found an increase in the death rate among those on supplementation.[39] It also found an increased death rate among those who continued to smoke.[39] 13-cis retinoic acid has also been found not to influence squamous metaplasia in another study.[40]

Beta-carotene as a lung cancer prevention agent has been reported in two large randomized trials–ATBC (alpha tocopherol beta carotene trial)[41] and CARET (carotene and retinol efficacy) trials.[42] Both of these

Table 1. TNM (Tumor, Node, Metastases) staging of non-small cell lung cancer.

Stage Group	TNM	Description	5-year survival
0	Carcinoma in situ		
IA	T1N0M0	-Tumor <3cm surrounded by lung or visceral -Pleura, not more proximal than labor bronchus (T1) -No lymph nodes or distant metastases	67%
IB	T2N0M0	-Tumor >3 cm or involves mainstem bronchus ->2 cm from carina -Invades visceral pleura -Lobar atalectasis (not entire lung atalectasis) (T2)	57%
IIA	T1N1M0	-T1 with involvement of ipsilateral hilar or peribronchial lymph -Nodes or direct extension to intrapulmonary nodes (N1) -No metastases	55%
IIB	TN1M0	-T2 & N1 as defined -No metastases	39%
	T3N0M0	-Direct invasion by tumor of chest wall, diaphragm, mediastinal pleura, parietal pericardium -In mainstem bronchus <2cm from carina -Atalectasis of entire lung (T3) -No lymph nodes or metastases	38%
IIIA	T3N1M0	-T3 & N1 as defined -No metastases	25%
	T1-3N2M0	-T1, T2, T3 as defined -Involvement of ipsilateral mediastinal or subcarinal nodes (N2) -No metastases	23%
IIIB	T4anyNM0	-Involvement of heart, mediastinum, great vessels, trachea, esophagus, vertebral body, carina -Malignant pleural or pericardial effusion -Satellite tumor nodule in ipsilateral tumor bearing lobe of the lung (T4)	7%
	AnyTN3M0	Metastases to contralateral mediastinal, or hilar nodes, ipsilateral or contralateral scalene nodes or supraclavicuar nodes	3%
IV	AnyT AnyN M1	Presence of distant metastases	1%

Adapted from Mountain, CF[45] and Mountain, CF & Dressler CM[132]

trials found a detrimental effect of beta-carotene in individuals on supplemental beta-carotene, showing a higher risk of lung cancer. This harmful effect was increased in heavy smokers[41,42] and clearly established that beta-carotene is harmful in smokers. Other dietary supplements have been reported to have a beneficial effect on lung cancer risk and are currently being tested in randomized studies.

Diagnosis

Lung cancer should be suspected in chronic smokers with protracted or new onset respiratory symptoms. The work-up usually starts with a chest X-Ray and if abnormal should lead to a computer tomographic scan. Further diagnostic work-up depends upon the location of the tumor–central tumors are best approached with a bronchoscopy, which allows for direct visualization of the airways as well as tumor, and permits biopsy material to be obtained for histologic diagnosis at the same time. Peripheral tumors can be biopsied via a transthoracic approach under CT or ultrasound guidance. Further invasive techniques including thoracoscopy, mediastinoscopy, and thoracotomy are reserved for those in whom the initial diagnostic techniques mentioned above fail to yield a diagnosis. Even though sputum cytology is a non-invasive method of establishing a diagnosis, negative sputum cytology does not rule out lung cancer. In experienced hands sensitivity

and specificity of sputum cytology in diagnosis of lung cancer may approach 0.66 and 0.99 respectively.[43]

Staging and Prognosis

The prognosis and management of lung cancer is critically dependent on appropriate staging. The work-up should include a detailed history and physical examination, chest X-ray, computed tomographic scan of chest and upper abdomen including liver and adrenals, serum chemistries including renal and liver function tests, serum calcium, and alkaline phosphatase. If history, physical examination or blood tests (calcium, alkaline phosphatase) suggest bone or central nervous system spread, a bone scan and CT scan of the brain should be obtained.[44] Pulmonary function testing and invasive mediastinal staging are reserved for those being considered for curative surgical resection or radical radiation therapy. Staging of non-small cell lung cancer (NSCLC) utilizes the Tumor, Node Metastases (TNM) system as revised in 1997 (Table 1).[45]

The prognosis of NSCLC depends upon extent of disease (stage), performance status, and weight loss. As alluded to before, despite extensive research the 5-year overall survival for NSCLC has remained remarkably constant at 14% in past the 20 years. Even in stage I patients undergoing curative surgical resection, the 5-year survival is only 60%.

Management of NSCLC

Surgical resection is the only potentially curative treatment of NSCLC. Unfortunately, it can only be offered to a minority of patients since approximately two-thirds to three-fourths of patients with NSCLC will present with advanced and potentially unresectable disease. Management depends upon the stage of disease, and surgery can be offered to those patients presenting with stage IA to stage IIIA disease who can tolerate surgery. Those with more advanced stage disease are offered chemotherapy, radiation therapy, or chemoradiotherapy. Some patients presenting with stage III disease, particularly those with stage IIIA, may be offered pre-operative chemotherapy or chemoradiotherapy to downstage the disease in an effort to render the disease surgically resectable.

Surgery

Even though surgery is curative, only one-third to one-fourth of patients present with an early enough stage to be offered surgical resection. In addition, comorbid conditions, especially those caused by tobacco smoking, namely coronary artery disease and chronic obstructive pulmonary disease, may make surgical resection technically difficult or impossible.

Patients being considered for surgical resection undergo a more rigorous pre-operative work-up, which may include computed tomographic or magnetic resonance imaging of the brain as well as positron emission tomography, in addition to pulmonary function testing.

Several retrospective and prospective studies have revealed a sensitivity and specificity of 85% and 88%, respectively, for mediastinal lymph node involvement with positron emission tomography (PET).[46] The sensitivity and specificity are even higher with use of both computer tomography and PET.[47]

Pulmonary function testing with a predicted post-operative residual forced expiratory volume (FEV1) of at least one liter is mandatory before considering surgical resection. Adequate surgical resections include lobectomy and/or pneumonectomy.

The role of post-operative radiation therapy remains controversial, and while some studies suggest a decrease in local recurrence rate without any impact on overall survival,[48] others have reported a detrimental effect on overall survival from post-operative radiation therapy with a 21% increase in the relative risk of death particularly in those with resected stage I disease.[49] The decision to offer post-operative radiation therapy should be individualized but should be strongly considered for those with positive or very close surgical resection margins or those with N2 disease.

Until recently post-operative chemotherapy did not have a defined role after surgical resection, but recently 4 large randomized controlled trials and a meta-analysis have demonstrated a clear benefit with post-operative chemotherapy.[50-53]

Radiation Therapy

Radiation therapy in the management of NSCLC may be offered with a curative intent to those with early stage disease deemed medically unfit to undergo anesthesia and/or surgical resection.[54,55] Patients with stages I-II treated with radiation therapy alone at a dose of at least 6000 cGy may achieve 5-year survivals of 10% to 27%.[55,56]

For patients with stage III disease, those with unresectable stage IIIA or stage IIIB disease excluding malignant pleural effusion, radiation therapy along with chemotherapy constitutes the standard of care (Table 3).[57,58] Until recently a sequential approach with two cycles of cisplatin-based chemotherapy followed by radiation was considered standard of care based on data published by the Cancer and Leukemia Group B

Table 2. Selected studies of neo-adjuvant and adjuvant strategies in non-small cell lung cancer

Study	Treatment	Comments
Neo-adjuvant Chemotherapy		
Roth[66]	Surgery and radiotherapy vs. cisplatin and etoposide before and after surgery	Increased 3-year survival with chemotherapy (56% vs. 15%)
Rosell[133]	Surgery and radiotherapy vs. mitomycin, ifosfamide and cisplatin before surgery and radiotherapy	Increased median survival with chemotherapy (26 mo vs. 8 mo). Lower then expected survival in surgery arm
Depierre[69]	Mitomycin, ifosfamide, cisplatin before surgery and radiotherapy vs. surgery and radiotherapy	Survival benefit at 1 and 4 years in early stage (N0 and N1). No benefit in N2
Adjuvant chemotherapy		
Holmes[134]	Cyclophosphamide, adriamycin, cisplatin vs. immunotherapy	Improved survival with adjuvant chemotherapy
Lung Cancer Study Group[135]	Cyclophosphamide, adriamycin cisplatin and radiotherapy vs. radiotherapy	Improved 1-year survival with adjuvant chemotherapy
Keller[136]	Cisplatin, etoposide and radiotherapy vs radiotherapy	No benefit with chemotherapy
Tonato[137]	Mitomycin, vindesine, cisplatin vs. observation	Stage I, II IIIA. At median follow up of 63 month no benefit in overall or event free survival
International Adjuvant Lung Cancer Trial[50]	Cisplatin based chemotherapy vs. observation	4% absolute increase in survival at 5 years
Strauss[70]	Paclitaxel and carboplatin vs. observation	Stage IB only. Overall survival at 4 years 71% vs. 59% in favor of adjuvant chemotherapy
Winton[53]	Cisplatin and vinorelbine vs. observation	Stage IB and II. Overall survival 94 mo vs. 73 mo in favor of adjuvant chemotherapy
Hamada[51]	UFT vs. observation	5- and 7-year survival rates improved with UFT

(CALGB) and the Radiation Therapy Oncology Group (RTOG).[59,60] However, the RTOG has reported the results of a randomized trial comparing this sequential approach to concurrent chemo-radiotherapy using the same chemotherapy with an improvement in median survival from 14 months with a sequential approach to 17 months with a concurrent approach.[61] A Japanese randomized trial using mitomycin, vindesine, and cisplatin has also shown improvements in 2-, 3-, 4-, and 5-year survival when radiatiotherapy was delivered concurrently with chemotherapy compared to a sequential approach.[62] The toxicity is understandably higher but concurrent chemoradiotherapy should be considered for patients with unresectable stage IIIA and IIIB patients with good performance status.

Radiation therapy is an excellent palliative option for control of pain, hemoptysis, and bronchial obstruction with post-obstructive pneumonia.

Chemotherapy

As mentioned, chemotherapy is not only offered in the post-operative adjuvant setting and as a neo-adjuvant approach to down-stage the disease but, a large majority of those who present with advanced stage (stage IIIB and IV) as well as those who relapse after resection, are offered this modality. As such, as many as 80% to 90% of all NSCLC patients may become candidates for chemotherapy during the course of their disease.

Pre-operative Chemotherapy

Pre-operative (neo-adjuvant, induction) chemotherapy may be offered to a selected group of patients with marginally respectable tumors, who have good performance status. Four randomized trials have addressed this issue (Table 2). Two of these were too small to draw useful conclusions[63,64] but studies by Rosell[65] and Roth[66] demonstrated an improvement in 2- and 5-year survival in those receiving pre-operative chemotherapy. Updated results from both these studies have

Table 3. Selected studies of chemotherapy and biologic therapy in advanced disease.

Study	Treatment	Remarks
Chemotherapy and radiotherapy in inoperable disease		
Dillman[57]	Cisplatin, vinblastine and radiotherapy vs. radiotherapy alone	Improved 1-,2-,3-,7-year survival with chemotherapy
Sause[58]	Cisplatin, vinblastine and radiotherapy vs. radiotherapy	Improved survival with chemotherapy
Curran[61]	Cisplatin, vinblastine given concurrently with radiotherapy vs. sequentially	Improved median survival with concurrent approach
Chemotherapy for advanced disease		
Schiller[81]	Carboplatin and paclitaxel vs. cisplatin and paclitaxel, cisplatin and gemcitaine, and cisplatin and docetaxel	Overall survival equal in all groups, longer progression survival but more toxicity in gemcitabine arm
Biological therapy in advanced disease		
IDEAL 1[103,104]	Gefitinib as second line vs. observation	20% response rate, symptom improvement
IDEAL2[138]	Gefitinib as 3rd and 4th line vs. observation	10% response rate symptom improvement
INTACT 1 and 2[106,107]	Chemotherapy vs. chemotherapy and gefinitib	No benefit with addition of gefinitib
TRIBUTE[108]	Chemotherapy vs. chemotherapy and erlotinib (OSI-774)	No benefit with addition of erlotinib in first line setting
TALENT[109]	Chemotherapy vs. chemotherapy and erlotinib (OSI-774)	No benefit with addition of erlotinib in first line setting

been reported and show a benefit with neo-adjuvant chemotherapy on long-term follow-up.[67,68] Despite limitations of these studies, it may be appropriate to offer 2 to 3 cycles of pre-operative chemotherapy to this patient group if surgical resection is deemed feasible with down-staging. Several ongoing randomized trials are addressing the issue of neo-adjuvant chemotherapy for earlier stage disease since a French trial by Depierre et.al. suggested a benefit for those patients with earlier stages treated with this approach.[69]

Post-operative chemotherapy

Recently, several randomized trials have conclusively provided conclusive evidence for a survival benefit with adjuvant chemotherapy after surgical resection (Table 2). The largest of these is the International Adjuvant Lung Trial (IALT) that included 1867 patients.[50] The accrual was stopped early with slowing of accrual as well as evidence of benefit on interim analysis. Adjuvant cisplatin based chemotherapy resulted in a 4.1% increase in overall survival at 5 years. There was also an improvement in disease-free survival from 34.3% to 39.4% at five years. Other trials demonstrating survival benefit with adjuvant chemotherapy include a Japanese randomized trial as well as a meta-analysis in stages IB and II adenocarcinoma in which post-operative fluorouracil-tegafur (UFT) was given orally for 2 years post-operatively.[51] The results are, however, not applicable at present outside Japan. Other more relevant studies include the CALGB and National Cancer Institute of Canada (NCIC) trials. The NCIC trial reported by Winton et al at the 40th annual meeting of American Society of Clinical Oncology in June, 2004 randomized patients with stage IB (T2N0) and stage II (excluding T3N0), after resection, to fourcycles of vinorelbine and cisplatin versus observation. In this trial overall survival was significantly prolonged in the adjuvant chemotherapy group (94 months vs. 73 months; HR=0.69, *P*=0.011). Relapse-free survival was also prolonged (not yet reached for adjuvant chemotherapy arm versus 46.7 months; HR=0.6, *P*=0.0003).[53] In the same meeting Strauss et al reported a CALGB trial in which patients with resected stage IB (T2N0) NSCLC were randomized to four cycles of paclitaxel and carboplatin versus observation. The hazard ratio for death from any cause was 0.62 (*P*=0.028) in favor of adjuvant chemotherapy. Overall survival at 4years was 71% versus 59% in the

chemotherapy and observation arms, respectively. Failure-free survival and lung cancer mortality were similarly improved with adjuvant chemotherapy. The hazard ratio for failure-free survival was 0.69 (P=0.035) in favor of the chemotherapy group and 4-year lung cancer mortality was 16% in the chemotherapy group versus 26% in the observation group.[70] In summary, platinum based adjuvant chemotherapy for three to four cycles may be considered standard of care after resection of stages IB to IIIA NSCLC.

Chemotherapy for Advanced Disease

Non small cell lung cancer presenting with stage IIIB and IV disease and relapsed NSCLC, with few exceptions, is incurable. In the past, few patients were offered chemotherapy for advanced NSCLC due to low response rates and toxicity. However, several studies, including meta-analyses, have demonstrated a modest gain of 2 to 4 months in median survival and a 1-year survival ranging from 10% to 20%.[71-73] Other studies have reported improvement of quality of life with chemotherapy which is highly significant in this patient population with limited survival.[74-76] This benefit is often restricted, however, to those who maintain a good performance status.

Several agents have shown single agent activity in NSCLC, but platinum has been used almost exclusively in single-agent chemotherapy for NSCLC. Phase III trials carried out in early 1990s, however, showed that cisplatin or carboplatin, when combined with second- and third-generation chemotherapeutic agents (paclitaxel, docetaxel, vinorelbine, gemcitabine) have a higher response rate, time-to-disease progression and, overall survival.[77-79] The Eastern Co-operative Oncology Group (ECOG) was the first to show the superiority of a newer generation platinum combination (paclitaxel and carboplatinum) over cisplatin and etoposide.[80] In 2001, Schiller et al reported the results of a large phase III randomized trial showing equal efficacy of four third-generation platinum combinations (Table 3).[81] A recent meta-analysis has, however, reported a slight superiority of gemcitabine-containing regimens over other platinum-based combinations.[82] It is appropriate to offer any of these two-drug combinations as first-line chemotherapy in this setting.[83] At present, no data exists to support a three-drug combination, which may offer a higher response rate with higher toxicity and without a survival benefit.[84,85]

The optimum duration of chemotherapy is another controversial issue and it is common practice to offer six cycles of chemotherapy to responding patients. At least three randomized trials have addressed this issue, and it appears that prolonging chemotherapy beyond three to four cycles adds toxicity without additional clinical benefit.[86-88]

Fit elderly patients seem to derive similar benefit from chemotherapy without increased toxicity and therefore should be offered similar therapeutic options as the younger patients.[89-91]

Patients who have responded to first-line platinum-based chemotherapy and maintain a good performance status can be offered second line docetaxel.[92,93] A recently reported phase III randomized trial has shown similar efficacy with pemetrexed in this setting.[94] Recently reported data also suggests that gemcitabine may have activity in second-line setting.[95,96]

Biologic Therapy

Non-small cell lung cancer cells over-express epidermal growth factor receptor (EGFR),[97,98] which provides these cancer cells a selective growth advantage with increased ability to grow, induce angiogenesis, and metastasize.[99-101] This results from activation of EGFR after binding to its ligand, which leads to phosporylation of the intra-cellular domain of the receptor. This leads to an increase in EGFR tyrosine kinase activity, resulting in an intra-cellular cascade of events leading to an increase in cell proliferation, a decrease in apoptotic potential, increased angiogenesis, and metastatic potential. Strategies to block this EGFR dependent tyrosine kinase pathway have included monoclonal antibodies, anti-sense oligonucleotides, and small molecules that block phosphorylation of the intra-cellular domain of EGFR receptor. Gefitinib (ZD1839, IRESSA) is the first such compound[102] and has shown a 10% to 20% activity in heavily pre-treated patients.[103,104] Most importantly, the responses are seen regardless of the level of EGFR expression.[105] Two large phase II trials in North America and Europe led to Food and Drug Administration (FDA) approval of gefitinib as a third-line agent (Table 3). Gefitinib has shown improvement in symptoms in up to 50% of patients.[104] Orally administered, the major toxicities are skin rash and diarrhea and an approximately 1% risk of developing potentially fatal interstitial lung disease (mostly in Japanese patients). Interestingly, development of some of these side effects, especially rash, may predict response to the agent, but this is not conclusive.

Table 4. Selected studies in management of small cell lung cancer.

Study	Treatment	Remarks
Limited Stage disease		
Perry[120]	Cyclophosphamide, etoposide/ adriamycin, vincristine alone vs. chemotherapy and early vs. delayed radiotherapy	Failure free survival overall survival improved with addition of radiotherapy
Takada[123]	Cisplatin and etoposide with concurrent vs. sequential radiotherapy	Improved 2- and 5-year survival with concurrent approach. More myelosuppression
Turrisi[124]	Chemotherapy with once daily vs. twice daily radiotherapy	Improved 5-year survival with twice daily radiotherapy (26% vs. 16%)
Extensive Stage Disease		
Fukuoka[118]	Cisplatin, etoposide vs. cyclophosphamide adriamycin, vincristine vs. both regimens alternating with each other	Response rate superior in etoposide containing regimens. Complete responses similar
Roth[119]	Cisplatin, etoposide vs. cyclophosphamide adriamycin, vincristine vs. both regimens alternating with each other	No difference among treatment groups
Noda[129]	Cisplatin and etoposide vs. cisplatin and Irinotecan	Median survival (12.8 vs. 9.4 months) and 2-year survival (19.5% vs. 5.2%) higher with irinotecan arm with increased incidence of diarrhea

The addition of gefitinib to first-line chemotherapy, on the other hand, has failed to show any benefit.[106,107] Similarly, the addition of erlotinib (EGFR inhibitor) to carboplatin and paclitaxel or cisplatin and gemcitabine did not confer a survival advantage over the same chemotherapy given alone in two recently reported randomized phase III trials.[108,109] There are several other biologic agents in various stages of development with promising data already reported on erlotinib[110] (EGFR inhibitor) and Avastin (vascular endothelial growth factor inhibitor). In a phase III trial of erlotinib versus placebo in a second- or third-line setting in patients with advanced NSCLC, Shepherd et al reported a prolongation of overall survival from 4.7 month with placebo to 6.7 months with erlotinib (P=0.001). There were statistically significant improvements in progression-free survival as well symptoms of cough, dyspnea, and pain.[110]

Patients with solitary brain metastases may achieve a 10% to 20% 5-year survival after resection of metastasis followed by whole brain radiotherapy.[111,112] Less convincing data also exist for resection of solitary adrenal metastases.[113,114] In both instances control of the primary tumor by surgery must be assumed.

Small Cell Lung Cancer

Small cell lung cancer (SCLC) is biologically distinct from NSCLC in its propensity to an early spread and have a rapid tumor doubling time. The staging schema is simpler, dividing the disease into limited and extensive stages. Limited stage is defined as disease confined to one hemithorax including ipsilateral mediastinal and/or supraclavicular disease, excluding malignant pleural effusion (operationally disease that can be confined within one tolerable radiation port). All other tumors are characterized as extensive. The staging work-up should include history and physical examination, laboratory evaluation, CT scans of chest and upper abdomen, bone and brain scans.[115] After a complete staging work-up only one quarter to a third of the patients will be identified as having limited disease.

Limited Stage Disease

Surgery is not considered a part of standard management of SCLC due to its propensity for early spread. On occasion, patients may undergo excision of a solitary pulmonary nodule that is subsequently identified as SCLC on pathologic examination. These patients should undergo mediastinal node dissection followed by combination chemotherapy.[16] Post-operative ra-

diotherapy should be added if mediastinal nodes are involved. All other patients should undergo combined modality therapy with chemotherapy and radiation therapy without surgery.

Randomized trials have established that combination chemotherapy is clearly superior to single- agent chemotherapy in small cell lung cancer.[116,117] Cisplatin and etoposide is the most commonly used chemotherapy regimen, although randomized trials in extensive stage disease have not demonstrated a survival benefit over the regimen of cyclophosphamide, vincrisitine and adriamycin.[118,119] Perry et al first reported a survival advantage with addition of thoracic radiotherapy to chemotherapy in limited stage disease (Table 4).[120] Meta-analysis have later confirmed a 5% reduction in the risk of death with the addition of thoracic radiotherapy.[121,122]

The timing of radiotherapy, early or late, is another area of intensive investigation and there is no consensus. It appears that concurrent chemotherapy and radiation offers an improved 5-year survival compared to a sequential approach.[123] Turrisi et al reported improved 5-year survival with hyperfractionated radiotherapy (twice daily fractionation) delivered concurrently with chemotherapy.[124] There are obvious problems of increased toxicity and the logistics of twice daily delivery of radiation. This approach is, therefore, not widely practiced as a standard of care.

Patients with limited SCLC who achieve complete remission may develop brain metastases as the initial site of relapse. Studies have reported up to a 50% incidence of brain metastases in this patient population.[125,126] Several studies failed to show a survival benefit with prophylactic cranial radiation (PCI) despite decreasing the risk of brain metastases. Even though there have been concerns about long-term neurologic sequalae, studies suggest that PCI does not result in clinically significant neuropsychologic sequalae,[127] especially if the radiation dose is limited to less than 3600 cGy in those without any neurologic deficit.[125] A meta-analysis has shown a clinically significant survival benefit (5.4% at 3 years) with the addition of PCI in those who achieve complete remission after chemotherapy and thoracic radiation.[128]

Extensive Stage Disease

Extensive stage disease is managed with combination chemotherapy. The combination of cisplatin and etoposide, or cyclophosphamide, adriamycin and vincristine appear equivalent in survival benefit, although a cisplatin-based regimen may offer higher response rates and improved toxicity profile (Table 4).[118,119] A recently reported randomized trial from Japan has reported improved response rates, median, and two year survivals with cisplatin and irinotecan compared to cisplatin and etoposide. The median and two year survivals were 12.8 months vs. 9.4 months and 19.5% vs. 5.2%, respectively.[129] There was less severe hematologic toxicity but more severe diarrhea with the irinotecan combination. Even though confirmatory trials of cisplatin and irinotecan are ongoing, at present it is appropriate to offer etoposide or irinotecan in combination with cisplatin as first-line therapy for extensive stage SCLC. Other agents with activity in SCLC include paclitaxel and topotecan. The addition of paclitaxel to cisplatin and etoposide has been studied and showed increased toxicity without survival benefit.[130] Topotecan has shown useful activity in the second-line setting and is currently being studied for use in first-line therapy.[131]

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