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Recent Trends in Management of Unresectable Non-Small Cell Lung Cancer (NSCLC)

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Lung cancer is a major health problem worldwide. It is etiologically related to smoking, the incidence is high and increasing in many countries, in both men and women. The treatment is so far not ideal and the results of various modalities of treatment available have reduced mortality only slightly. This is a review of the role of chemotherapy in treatment of lung cancer, with emphasis on the role of newer cytotoxic drugs in management of locally advanced and metastatic Non-small cell lung cancer (NSCLC); when definite curative surgery is not feasible.

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NSCLC is a significant health problem around the world. In the USA, NSCLC is the second most common cancer in both men and women, and the leading cause of death in both groups[1]. According to the publications of GCC cancer registry, lung cancer is the most common type of cancer among men in Bahrain and has the highest rate compared to other Gulf States with an Age Standardized Rate (ASR) at 22.6/100,000[2]. This is a review of the role of chemotherapy in the treatment of lung cancer.

Epidemiology

Incidence rates of lung cancer is continuing to increase in most countries of the world. It increases with age and is steadily increasing in both industrialized and developing countries. While efforts in early detection and adequate treatment have failed to reduce mortality significantly, the major cause of this disease is known to be cigarette smoking. Primary prevention through control of cigarette smoking is the most important measure for combating the disease[3].

Most patients with lung cancer are diagnosed between 35 to 75 years of age with a peak at 55-65 years. More than 80% of lung cancer among men is related to cigarette smoking. The incidence and mortality rates from lung cancer among women are now rising faster than men and lung cancer is already the leading cause of cancer deaths among women in some countries.

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Less than 10% of lung cancer patients survive 5 years and 80% are dead within a year of diagnosis[1]. Cessation of cigarette smoking is followed by a decrease in the risk of lung cancer and the mortality rate from lung cancer would return to the level of nonsmoker within 20 years. In patients with metastatic disease, median survival is only 4 months for patients treated with best supportive care alone.

Pathology

Lung cancer usually originates from the epithelium of the primary and segmental bronchi and less frequently from the peripheral small bronchi. There are many histological types of lung cancer and currently it is divided into either Small Cell (20-25%) or Non-Small Cell Lung Cancer (75-80%).

This review is concerned only with NSCLC that includes many sub-types[3]:

Squamous Carcinomas are the most common (40-50%), tend to be central and occur primarily in men. These may be highly differentiated with keratin formation or anaplastic.

Adenocarcinomas make up 25-30%. They are often peripheral and may present as pleural effusion. They are less often associated with smoking than other types of lung cancer.

Large Cell Carcinomas occur in only 10% of cases. They may appear either centrally or peripherally.

Other types are uncommon, it include bronchiolo-alveolar carcinomas, carcinoid tumours and mucoepidermoid carcinomas.

Staging of NSCLC

TNM Clinical Classification system and stage Grouping.

Table 1**. Summary of TNM Clinical Classification System for NSCLC**

TX	Positive cytology
T1	≤3 cm
T2	> 3 cm, main bronchus 2 cm or more from carina, invades visceral pleura, partial atelectasis
T3	chest wall, diaphragm, pericardium, mediastinal pleura, main bronchus < 2 cm from carina, total atelectasis
T4	Mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebra; separate nodules in the same lobe, malignant effusion
N1	Ipsilateral peribronchial, ipsilateral hilar

N2	Ipsilateral mediastinal, subcarinal
N3	Contralateral mediastinal or hilar, scalene or supraclavicular
M1	Includes separate nodule in different lobe

T = Tumour (primary)
N = Node
M = Metastases

Table 2. **Stage Grouping for NSCLC**

Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Management of NSCLC

Principles of Treatment:

Surgery is the treatment of choice for early stage of NSCLC (T_{is}, T_1 and T_2, N_0, M_0) with the hope of cure. Lobectomy is preferred when feasible. About 25% of all patients can have a resection with some hope of cure. Patients with T_2, N_1 lesions respond less favorably to surgical treatment.

Recently, patients with clinical N_2 disease have been treated with cytotoxic drugs (Neo-adjuvant Chemotherapy) prior to surgery and some responders have been converted to "operable" and thus possibly "curable"[1-3].

In some patients, radiation therapy may be given with curative intent. These are usually patients for whom surgery is a risk. But radiation therapy may cause pulmonary fibrosis and cardiac damage.

Radiation therapy is used for palliation of symptoms such as persistent cough, pain, haemoptysis and hoarseness. Radiotherapy is also utilized to relieve bronchial obstruction, superior vena cava compression and to control pain due to bone or brain

metastases. However, the use of pre-operative irradiation does not improve the rate of resectability or curability of lung cancer.

Chemotherapy, usually a platinum-based regimen, is appropriate for selected patients with unresectable, locally advanced and metastatic NSCLC. A detrimental effect on survival was observed with older alkylating agent-based regimens. In patients with unresectable stage III NSCLC, two or more cycles of cisplatin-based chemotherapy with or followed by radiation has been proven to enhance survival; ongoing maintenance chemotherapy is of unproven benefit. Chemotherapy should be administered for no more than eight cycles in patients with stage III or IV NSCLC. Delayed chemotherapy until symptoms develop may negate the survival benefits of treatment. There is no current evidence that second-line chemotherapy improves survival in patients with non-responding or progressive NSCLC. Histological type of NSCLC is not an important prognostic factor in these patients and the role of newer prognostic factors (eg. P53 mutation) in clinical decision-making is investigational.

Treatment of Unresectable NSCLC

Chemotherapy in association with definitive-dose radiotherapy prolongs survival in patients with locally advanced and surgically unresectable NSCLC. These patients frequently have extensive disease and compromised performance status, often associated with significant co-morbid conditions.

Physicians have an obligation to help patients make the right decision. The anticipated outcome, the potential toxicity and inconvenience of therapy is critical and should be discussed with the patients[6].

Unresectable Stage III NSCLC

Traditionally, such patients were treated with thoracic radiotherapy with 5-year survival rates of 4% to 8%. In a recent meta-analysis of all randomized trials of radiotherapy with or without cisplatin-based chemotherapy, the addition of chemotherapy led to a 13% reduction in death risk, although the absolute survival advantage at 2 years was a modest 4%[7]. In a randomized trial in the early eightees, three times as many patients were alive at 5 years after combined modality compared with patients receiving radiation alone (17% versus 6%)[8, 9].

Controlled studies of concurrent chemo-radiotherapy with daily low-dose, less toxic administration of drugs have been documented to prolong survival compared with radiation alone[10,11]. Based on these data cisplatin-based chemotherapy regimens became the standard treatment for locally advanced NSCLC. Chemotherapy also demonstrated both improvement in cancer related symptoms and to be cost effective.

The results of a recent meta-analysis of a large co-operative group experiences indicate survival is most improved with platinum based chemotherapy[7,16]. Another recent meta-analysis addressed survival benefits of single agent chemotherapy compared with

combination chemotherapy and nine controlled trials that enrolled 1,493 patients were included in the analysis. The estimated pooled odds ratio was 0.80 in favor of combination chemotherapy[17].

The "best" platinum–based regimen is not well defined. Numerous combinations have been prospectively compared using older agents, with no single regimen emerging as the superior combination. Recently published prospective trials indicate relatively new drugs as vinorelbine or paclitaxel in combination with cisplatin can improve survival beyond that achieved with more established regimens such as cisplatin plus vindesine[14] or cisplatin plus etoposide[13], respectively.

Regarding the selection of drugs, uncontrolled studies suggest that cisplatin and carboplatin may have comparable efficacy against NSCLC[25,26].

Stage IV NSCLC

Chemotherapy modestly improves median survival in patients with distant metastatic NSCLC compared with best supportive care, but is not curative. The results of three recently published meta-analyses indicate that cisplatin-based chemotherapy yields an improvement in median survival of approximately 6 to 8 weeks in stage IV NSCLC[6,7,12]. The one year survival rate is increased from 15% to 25%. Compared with supportive care alone, cisplatin-based chemotherapy produced an absolute improvement in survival of 10% at one year[7].

These meta-analyses do not include the most recent randomized data evaluating newer drugs. In a recent randomized trial, two dose levels of paclitaxel given in conjunction with cisplatin have produced significantly higher response rates and borderline survival improvement compared to etoposide with cisplatin. No survival advantage with higher dose, but more toxic with Paclitaxel regimen effect[13].

Both single-agent vinorelbine (navelbine) and single-agent cisplatin have been found to produce survival rates inferior to cisplatin plus vinorelbine in two recently completed phase III trials.[14,15] These randomized trials show that one year survival rates of 35% to 40% are achieved with these newer regimens.

Recently, a number of new non-platinum compounds have demonstrated activity in NSCLC, including paclitaxel, docetaxel, gemcitabine, navelbine, irinotecan and topotecan. Response rates for these new compounds have ranged from 12-42% in phase II and III trials[19-21].

Table 3. **Summary of Phase I/II studies with non-platinum-based doublets in NSCLC**

Author	**Drugs**	**Patients**	**Response Rate**	**Other**
Takeda[19]	Tax/CPT-11	32	34%	1 yr survival=38%
Herbst[20]	Gem/Navel	56	42%	MS=32.4 wks

Kourousis[21]	Tax/Navel	46	37%	1 yr survival=24%
Trillet-Lenoir[22]	Tax/Navel	39	27%	
Krug[23]	Tax/Navel	35	54%	1 yr survival=86%
Rosen	Paclitaxel/Gem	--	22%	Second line
Spiridonidis[24]	Tax/Gem	21	43%	Phase I
Georgoulias[25]	Tax/Gem	51	37.5%	1 yr survival=51%

Tax = Taxotere, CPT-11 = Irinotecan, Gem = Gemcitabine, Navel = Navelbine, MS= Median Survival

Investigators have developed many non-platinum -based doublets in the hope of maintaining activity with lower toxicity. In NSCLC, non-platinum- based doublets that have demonstrated interest include Taxotere Gemcitabine, Taxotere Navelbine, Gemcitabine Nabelbine, Taxotere Irinotecan and Gemcitabine Irinotecan. The results of many randomized phase I/II studies with non-platinum doublets showed high response rate ranging from 22% to 54% with survival advantage at one year (Table 3)[21-25].

CONCLUSION

The overall management of lung cancer is multidisciplinary; the change noted recently in management of unresectable NSCLC is mostly with the introduction of newer cytotoxic drugs. These drugs are given in combination with or without cisplatin, which is considered the standard treatment. The response rates are improving but the results on survival rates are still modest. Further trials and efforts are needed to improve on overall survival and quality of life of these patients.

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