From the Desk of Director Research

The 8th Annual International Conference ‘RGCON 2009’ being organized by the Institute from March 27th to 29th, has its main theme as “Thoracic Cancers: New Frontiers and Horizons.” Its scientific sessions have been so designed as to highlight the latest advances in multimodal management of lung and esophageal cancers for practising oncologists and primary healthcare physicians. This special issue of Cancer News highlights the latest developments in the field of Thoracic Cancers.

India has one of the widest Compulsory Licensing (CL) provisions in the world that enable generic companies to seek a CL and supply more affordable generic drugs. A special gratitude to Dr K Satyanarayana and Dr S Srivastava, Department of Health Research, Indian Council of Medical Research, for contributing the “Guest Article” on Compulsory Licensing as a Tool to Promote Access to Cancer Drugs.

“In Focus” gives an Overview on Tumor Board, a forum for multidisciplinary discussions regarding diagnostic and treatment aspects of cancer patients in the Institute.

A special thanks to Siemens Medical Solutions for supporting this issue of Cancer News. We also gratefully acknowledge the contributions made by the Oncologists and DNB candidates of this Institute. Views and suggestions from readers on Cancer News are welcome.

Dr (Mrs) Ira Ray


**LUNG CANCER**

**Introduction**

Lung cancer is the leading cause of cancer deaths in both men and women throughout the world. It is a disease of uncontrolled cell growth in tissues of the lung, which may lead to metastasis. The higher proportion of mortality in this cancer is attributed to the fact that majority (70%) of the patients are locally advanced or metastatic at presentation. The disease is rarely curable, and even with advancements in diagnosis and treatment, the overall 5-year survival rate is 15%. The two major forms of lung cancer are non-small cell lung cancer (NSCLC; about 85% of all lung cancers) and small cell lung cancer (SCLC; about 15% of all lung cancers).

Compared to a decade ago, scientists have made significant progress in understanding the molecular biology of lung cancer and the potential therapeutic targets in the disease. New techniques both in surgery and radiotherapy, are gaining grounds with increasing use of combined modalities consisting of surgery, chemotherapy, radiotherapy and targeted treatment. The molecular advances may lead to personalized prevention and treatment of this global menace.

**Lung Cancer Burden**

Lung cancer is the most common cancer worldwide, affecting over a million people every year. The global incidence of lung cancer is increasing at a rate of 0.5% per year. It is estimated that almost 170,000 new cases of lung cancer are diagnosed in the US each year. In Europe, the annual number of newly diagnosed patients exceeds 200,000, contributing to about 20% of all cancer deaths. It is estimated that, in India, about 30,000 new lung cancer cases are registered every year. The annual crude incidence rate of lung cancer is 0.1 per million of urban population in India. It contributes to 28% of all cancer deaths each year. Approximately 400 patients of lung cancer report to Rajiv Gandhi Cancer Institute and Research Centre every year.

**Risk Factors**

Cigarette smoking is responsible for 90% of the cases of lung cancer. The risk of dying of lung cancer is 22 times higher for male smokers and 12 times higher for female smokers compared with those who have never smoked. The risk of developing lung cancer is directly related to the duration of smoking and persists for a long time, even after having ceased smoking. Passive smoking also leads to increased incidence of lung cancer. Numerous studies show a 30% increase in risk among the spouses of smokers. The chemicals implicated in its causation include tar, soot (contains benzo(a)pyrene), arsenic, chromium, nickel, asbestos and radon.

**Pathology**

There is increasing evidence that lung cancer is derived from pluripotent stem cells that are capable of expressing various phenotypes. This epithelial stem cell in normal histogenesis differentiates to pseudostratified ciliated goblet columnar cells, neuroendocrine cells and type 1 and type 2 pneumocytes that line the alveoli. The cells that are capable of division can express hyperplastic, metaplastic or neoplastic change. NSCLC includes squamous cell carcinoma, adenocarcinoma, large cell carcinomas, adenosquamous carcinomas, bronchial carcinoids and other rare tumors. The American Joint Committee on Cancer TNM staging is used for the staging of NSCLC. SCLC is often simply classified according to a two-stage system introduced by the Veterans’ Administration Lung Study Group (VALSG). In the VALSG system, limited stage is defined as disease confined to one hemi-thorax that can be encompassed in a single radiation portal. All other patients are considered to have extensive stage disease.

**Clinical Presentation**

The patient with carcinoma of the lung generally is a man above sixty, a heavy cigarette smoker and residing in an urban area. Early lung cancer often does not cause symptoms. As the cancer grows, common symptoms may include a cough that gets worse or does not go away, respiratory distress, chest pain, hemoptysis, hoarseness of voice, frequent lung infections, such as pneumonia, unexplained weight loss and anorexia. A high index of suspicion needs to be exercised if the respiratory complaints persist.

**Screening and Diagnosis**

Screening for lung cancer has been extensively studied using chest X-ray and sputum cytology but has not been consistently found to be beneficial. The introduction of low dose spiral Computed Tomography (CT) has reopened the debate with numerous studies showing increased detection of cancer at an early stage.
The investigations are aimed at (a) confirmation of diagnosis and histological sub-typing; (b) staging of the disease to determine the optimum line of treatment/operability; and (c) fitness for surgery, if indicated.

Performing a chest X-ray is the first step if a patient reports symptoms that may be suggestive of lung cancer. It may reveal an obvious mass, widening of the mediastinum, atelectasis, consolidation or pleural effusion. If there are no X-ray findings but the suspicion is high, a bronchoscopy and/or a CT scan may delineate the lung lesion.

The tissue diagnosis is obtained most often by sampling of intrathoracic tissues. Modern bronchoscopic and transthoracic puncture techniques are highly accurate in experienced hands and have an acceptable morbidity and negligible mortality. To obtain the diagnosis, bronchial biopsy, brushing and sputum aspiration are mostly used. For peripherally located tumors, broncho-alveolar lavage, transbronchial biopsy and/or image guided fine needle aspiration are used. Sensitivity for the diagnosis of peripheral primary lung cancer by Trunschscopic Needle Biopsy is 90%. CT guidance has a higher sensitivity as compared to fluoroscopic guidance.

Sputum cytology has a lower diagnostic yield, particularly in peripheral lung lesions and should be reserved for patients in poor general condition when bronchoscopy cannot be performed. More than a third of patients with lung cancer have a pleural effusion and a simple pleural tap with cell block analysis can yield the diagnosis rapidly in such cases.

Newer modalities of obtaining diagnosis, like bronchoscopic ultrasonography (USG), esophageal USG with fine needle aspiration and virtual bronchoscopy guided transbronchial needle aspiration are currently under evaluation. Gene expression profiling is another new development in the diagnosis of lung cancer.

Treatment

Non Small Cell Lung Cancer

Surgery, radiation therapy and chemotherapy are the three modalities commonly used to treat patients with NSCLC. For patients with localized disease (Stage I or II), surgery offers the best chance of cure. Lung sparing sleeve lobectomy, segmentectomy or wedge resection is preferred over pneumonectomy, as long as clear surgical margins are ensured. Video assisted thoracic surgery (VATS) is currently being investigated for diagnostic as well as therapeutic interventions in NSCLC. In Stage I NSCLC patients, VATS has equivalent survival rates as compared to open thoracotomy with the distinct advantage of minimal post-operative morbidity. Various studies have clearly shown the benefit of adjuvant chemotherapy (platinum-based doublet) after surgery for Stage II or III cancers.

In patients with locally advanced cancers not amenable to surgery, concurrent chemoradiation is considered to be the standard of care. A total radiation dose of 60-74Gy should be used in 2 Gy per fraction along with chemotherapy (Conventional fractionation schedule). The preferred concurrent chemotherapy regimes are Cisplatin/Etoposide or Cisplatin/Vinblastine. Endobronchial radiotherapy and interstitial brachytherapy with radon 222 are other modalities for effective focussed delivery of radiation to the neoplastic tissue.

4-D image guided radiotherapy (IGRT), stereotactic radiosurgery (SRS) and proton therapy are the new developments in radiotherapy for lung cancer treatment with the intent of minimal radiation exposure to normal tissues. IGRT takes lung motion during respiration into account. For early stage operable and resectable lung cancer, SRS is a non-invasive treatment using high dose precise irradiation to the tumor volume.

Patients with Stage IV disease who have a good performance status benefit from chemotherapy, the first line being a platinum agent (Cisplatin or Carboplatin) combined with a third generation agent (Gemcitabine, Paclitaxel, Vinorelbine and recently Irinotecan). Pemetrexed-platinum combination has recently been approved as first line regimen in non squamous lung cancers. In view of slightly differing toxicity profile, oncologiststend to individualize the chemotherapy regimen.

Targeted Therapy

Effective targeted agents have been developed in the treatment of NSCLC. Bevacizumab is a monoclonal antibody that blocks the vascular endothelial growth factor (VEGF). It has been approved for front line use in patients with unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC.

Erlotinib and Gefitinib are small molecule epithelial growth factor receptor (EGFR) tyrosine kinase inhibitors and have shown efficacy in the treatment of advanced lung cancers with EGFR mutations. They have been approved for use in 2nd line or 3rd line setting with
Maximum benefit seen in Asian, non-smoker females with adenocarcinoma.

2nd Line Therapy

Currently, Pemetrexed and Docetaxel are approved for the patients who have progressed after receiving first line therapy. The two agents have shown to be equal in efficacy with differing toxicity profiles.

Small Cell Lung Cancer

In comparison to NSCLC, SCLC has a more aggressive behavior with systemic metastasis at initial presentation. Local modalities, such as radiation therapy or surgery, are not the initial mode of intervention in SCLC. Combination chemotherapy is the mainstay of treatment. In limited stage SCLC, chemotherapy with Cisplatin & Etoposide and radiation therapy to chest and prophylactic cranial irradiation is the preferred sequence of treatment. In extensive stage SCLC, chemotherapy is the only mode of treatment with initial response rates approaching 70-80% but relapse within a median 2 years of cessation of therapy. Prophylactic cranial irradiation is nowadays being proposed in patients with extensive SCLC who have shown complete responses post-chemotherapy. There are currently no targeted agents effective against SCLC.

Prevention of Lung Cancer

Primary prevention of lung cancer plays a vital role in increasing survival rates and decreasing the costs of treatment. People should be effectively educated about the causal relationship of smoking and lung cancer. Tobacco control and treatment of nicotine dependence should be taken up as a prime responsibility of physicians. Chemoprevention is defined as the use of specific natural or synthetic chemical agents to reverse, suppress or prevent premalignancy from progressing to invasive cancer. A Phase 3 trial is evaluating the role of selenium and vitamin E for chemoprevention of lung cancer.

Key Points

- Lung cancer is one of the leading causes of mortality in women and men throughout the world.
- Majority of the cases (70%) of lung cancer are locally advanced or metastatic at the time of presentation.
- Cigarette smoking is responsible for about 90% of the cases of lung cancer while environmental factors like chemicals and radiation are responsible for only a minority of cases.
- Tobacco smoke contains more than 100 different mutagens and carcinogens. These carcinogens and mutagens cause DNA damage.
- At molecular level, the common abnormalities seen are increased expression of telomerase, EGFR, MYC and Cyclin D1 and decreased expression of P16, 1NK4A, p53 and RAR ã. Key usage of molecular biology of lung cancer is for prevention, early diagnosis, prognostic and therapeutic purposes.
- PET scan has become an important preoperative staging modality in lung cancer. Endoesophageal and endobronchial ultrasonography with Fine Needle Aspiration Cytology are emerging modalities for mediastinal staging.
- Presently, several studies are evaluating the role of lowdose spiral CT scan chest as a screening modality and some early results are promising.
- Surgery plays an important role in early stage NSCLC, but has limited role in the management of SCLC.
- Recently, addition of an anti-VEGF agent (Bevacizumab) has been shown to improve survival in metastatic NSCLC.
- Recently, EGFR inhibitors have been shown to be effective 3rd line agents.
- SCLC is an aggressive tumor. It tends to disseminate faster and is commonly associated with paraneoplastic manifestations.
- Novel agents, including camptothecins (irinotecan, topotecan), semi-synthetic vinca alkaloids (Vinorelbine), new antimetabolites (Gemcitabine) and taxanes (Paclitaxel, Docetaxel), have shown activity in SCLC.
- Pharmacogenomic studies are elucidating the genetic nature of differences in drug disposition and effects. This enhances the drug discovery process and provides a stronger scientific basis for optimizing drug therapy on the basis of each patient’s genetic constitution. ERCC, RRM-1 and thymidylate synthase expression levels are used to tailor the chemotherapeutic agent to be administered.
- Therapeutic vaccines, Stimuvax (targeting MUC-1) and MAGE 3 are currently being evaluated in Phase 3 clinical trials.
COMPULSORY LICENSING AS A TOOL TO PROMOTE ACCESS TO CANCER DRUGS

Introduction

The global disease burden is on the steady rise, with both communicable diseases (CD) and non-communicable diseases (NCDs) contributing to a significant proportion of morbidity and mortality [1-2]. With NCDs set to overtake CDs by 2015, there is a serious concern of the implication of such huge disease load along with healthcare costs for the chronic diseases [1]. While the public healthcare system largely takes care of people with infections such as tuberculosis, malaria, leprosy, etc, the cost of drugs for NCDs is borne by the patients [3]. Access to medicines is the most significant tool that the society possesses to prevent, alleviate, and cure diseases that are either preventable or to some extent easily treatable with a relatively small number of medicines [4].

One of the major reasons for lack of affordable healthcare is the high cost of drugs and hospitalization, especially for diseases like cancer which are on the rise in India and elsewhere in the world (see Table, P 7). Almost all the drugs available for cancers are marketed by multinational pharma companies which spend substantial amount to discover and market the drugs. As these drugs enjoy patent protection (typically 20 years), the innovator companies enjoy monopoly for fairly long periods even after accounting for a few years for clinical trials. High drug prices set by the pharma companies, ostensibly to recover R&D costs, are considered a major barrier for affordable care for cancer. Prohibitive drug prices are often the result of strong intellectual property protection [5]. Governments in developing countries attempted to bring down the price of medicines which have come under pressure from industrialised countries and the multinational pharmaceutical industry.

TRIPS and Intellectual Property Protection

Intellectual property rights are governed by global treaties as the Trade Related Intellectual Property Rights (TRIPS), an international agreement that mandates uniform patent rules for all member countries. The TRIPS agreement sets out minimum standards for the protection of intellectual property, including patents on pharmaceuticals with the belief that patent system is a social policy tool for granting protection, for the benefit of society, by promoting innovation in exchange for a limited monopoly. As per TRIPS, all member countries, including India, are expected to provide product patent protection for 20 years for all drugs patented in respective countries and amend their national laws to be in conformity with the TRIPS agreement. Since 2005, India became fully TRIPS-compliant with its patent laws suitably amended. Overall, the TRIPS agreement is considered to impact the access to drugs in poor countries as drug prices are set by the pharma companies and not by the paying capacity of public [1,6]. Most poor countries like India are affected as a large number of people depend upon the public healthcare systems that do not provide medicines, especially for chronic diseases like heart disease, cancers, diabetes, etc. To address such anomalies, the TRIPS agreement has a lot of ‘flexibilities’ that sovereign countries can use to ensure access to medicines [3]. This has been reiterated by the Doha Declaration [6,7]. These flexibilities include, among others, compulsory licensing.

What is Compulsory Licensing?

Compulsory Licensing (CL) is a procedure whereby a government can allow any company, agency or designated person the right to make a patented product, or use a patented process under license, without the consent of original patent holder [8]. Such licences may constitute an important tool to promote competition as well as increase the affordability of drugs by ensuring the patent owner to obtain compensation for the use of the invention. The TRIPS agreement provides special rules for compulsory licences granted to government agencies or contractors. Countries’ national legislation may eliminate a patent owner’s right to seek an injunction to bar the government or a government contractor from using its patent, allowing the patent owner only the right to seek compensation [9].

CL and New Patent Law of India

India has one of the broadest CL provisions in the world that enable generic companies to seek a CL for a drug considered unavailable in adequate quantities locally. If the government feels the price is not reasonable, and if the patent holders claims that they have no manufacturing facilities in India, in that case the government can permit a local firm to make and sell the patented product at an affordable cost. Most patented drugs of multinational drug firms are imported today.
The amended Indian Patent Act (2005) has also not prohibited issuing the CL on generic drugs. In fact, the scope of CL has been broadened to be fully TRIPS-compliant and in accordance with the Doha Declaration [7]. The Indian Patent Law provides for adequate powers to the Controller General of Patents to issue compulsory licences to deal with extreme and/or urgent situations [10]. Following are the important sections in the Indian Patent Act that deal with CL:

A) Section 84: It states about the abuse of patent as a monopoly and to makes way for commercial exploitation of invention by an interested person. Under this section, any person can make an application for grant of CL for a patent after three years from the date of grant of that patent, on any of the following grounds: (a) The reasonable requirements of the public with respect to the patented invention have not been satisfied. (b) The patented invention is not available to the public at a reasonably affordable price. (c) The patented invention is not worked in the territory of India. Moreover, Section 89 also specifies and explains the general purposes of granting compulsory licence under Section 84.

B) Sections 92 (1) and 92 (3): Both these sections enable the Central Government and the Patent Controller, respectively, to deal with circumstances of national emergency or circumstance of extreme urgency related to public health crisis by granting relevant compulsory licences. This provision is also as per the Doha Declaration [7].

C) Section 92 A: Provides for CL of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems. Thus, this section is an “enabling provision” for export of pharmaceutical products to any country having insufficient or no manufacturing capacity in the pharmaceutical sector in certain exceptional circumstances, to address public health problems. Such a country has either to grant compulsory licence for import or issue a notification for import into that country. Although a number of developing countries have made use of CL to enable the supply of more affordable generic drugs in recent years, but relatively few compulsory licences have actually been effectively materialized despite the provisions for compulsory licences in many national laws. Basically, the impact of CL mechanism, especially on affordable drugs, cannot be measured by mere granting of CL.

**CL in India**

After the Indian Patent Act (2005) was amended, providing new provisions on CL in tune with Doha Declaration, the first application for CL in India was filed by M/s Natco Pharmaceuticals, Hyderabad, for the anti-cancer drug Tarceva. This application has put Indian Patent Act under the scanner. Tarceva is a novel therapy to treat people with non-small cell lung cancer, whose cancer has recurred or not responded to at least one course of chemotherapy. It is the brand name of Erlotinib, a group of cancer drugs known as epidermal growth factor receptor inhibitors. Tarceva is believed to prolong and improve the quality of life. Erlotinib is also being tried out as a possible treatment for many other cancers, including pancreatic cancer, ovarian cancer and cancer of the head and neck as part of a research trial. In brief, Tarceva is an important drug for treatment of cancer. Tarceva is a patented product of the Swiss drug major Roche. The cost of Tarceva

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug (Chemical)</th>
<th>Price</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech &amp; Hoffman La Roche</td>
<td>Herceptin (Trastuzumab)</td>
<td>Rs 1.3 lakh per injection</td>
<td>10-15</td>
</tr>
<tr>
<td>Hoffman La Roche</td>
<td>Matbhera (Rituximab)</td>
<td>Rs 1 lakh per injection</td>
<td>10-12</td>
</tr>
<tr>
<td>Genentech</td>
<td>Rituxan (Rituximab)</td>
<td>Rs 1 lakh per injection</td>
<td>10-12</td>
</tr>
<tr>
<td>Amgen</td>
<td>Neupogen (Filgrastim)</td>
<td>Rs 3,200 per injection</td>
<td>Nolimit</td>
</tr>
<tr>
<td>Imclone Systems</td>
<td>Eributix (Cetuximab)</td>
<td>Rs 17,584 per injection</td>
<td>4-5 in 1cycle</td>
</tr>
<tr>
<td>OSI Pharma &amp; Hoffman La Roche</td>
<td>Tarceva (Erlotinib)</td>
<td>Rs 4,800 per tablet</td>
<td>Not known</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Zoladex (Goserelin acetate)</td>
<td>Rs 8,910 per injection</td>
<td>Not known</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Hycamtin (Topotecan)</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Novartis</td>
<td>Gleevec (Imatinib-mesylate)</td>
<td>Rs 1.2 lakh for a month</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Table: Prices of Drugs on Cancer
is as high as Rs 4,800 per tablet, which on an average would amount to Rs 1.5 lakh per year per patient. Two Indian drug makers, Natco Pharma and Cipla are both trying to introduce cheaper generic versions of the patented medicine to help those who cannot afford the patented drug. Natco plans to price the drug at about one-fifth of original price, i.e Rs 1,000 per tablet. Cipla plans to sell the tablet at Rs 1,600. The drug Tarceva was jointly developed by Roche, OSI Pharmaceuticals and Genentech and the patent for Erlotinib was granted in the US (5,747,498).

Role of Generic Manufacture

Indian generic manufacturer M/s Natco Pharma has filed an application for CL for Tarceva (Erlotinib), primarily for the export of 30,000 tablets to Nepal and has offered Roche a five percent royalty. Natco is seeking a CL under Section 92A of the Indian Patent Act.

The drug major Cipla is also fighting a battle in Indian High Court on the same drug. Considering the Roche vs Cipla case, Roche was granted marketing rights in India for Tarceva in July 2005. That means Cipla couldn’t use the pre-2005 exception to sell a generic version. An Indian patent for Tarceva was granted in July 2007. Cipla did not challenge the patent with a pre-or post-grant opposition with the Indian Patent Office. Cipla is a large supplier of medicines to the domestic market and has made the move to supply Erlotinib in India at a third of the cost of patented drug.

Recently, Delhi High Court (HC) rejected an injunction plea by the Swiss drug major to prevent Cipla from manufacturing and selling generic version of Tarceva. However, it is only an interim order and the HC is expected to deliver its final judgment on the completion of hearings. The court meanwhile has directed Cipla to keep a separate record of the sale of its generic anti-cancer drug.

Provisions under the 2001 Doha Declaration of the WTO [7] permit CL to export drugs to less developed countries. Only the importing country must notify the WTO’s Council for TRIPS of the name and expected quantity of the product, ensure that the importing country has insufficient or no manufacturing capacity for the product, and confirm that it has granted or intends granting a CL. In all the cases, it is the responsibility of the WTO member-country to ensure and prove that its intent behind CL is in public interest. During 2006, Thailand issued a compulsory licence for Merck and Co.’s HIV/AIDS drug Efavirenz in a bid to cut the growing healthcare costs. The Thai government then argued that products imported from India cost half that of Strocin, Merck’s patented drug. If Tarceva’s case is successful, it will only be the second “Doha” licence. The first Doha based compulsory licence for export of GSK’s ARV drug Trivir was from Canada to Rwanda.

References

7. WT/MIN(01)/DEC/2 (2001): Declaration on the TRIPS agreement and public health.

(The Institute appreciates Dr K. Satyanarayana and Dr S Srivastava, Intellectual Property Rights Unit, Department of Health Research, Indian Council of Medical Research, for their contributions to this ‘Guest Article’ on Compulsory Licensing as a Tool to Promote Access to Cancer Drugs)
The American Society for Clinical Oncology (ASCO) has announced its annual list of major advances in cancer treatment and prevention in the year 2008. Only studies that significantly altered the way a cancer is understood or had an important impact on patient care, were included. The choices come from the cancer specialists who make up the ASCO’s editorial board. The twelve major advances according to ASCO are:

**Erbitux for Lung Cancer**
Advanced non-small-cell lung cancer is a grim diagnosis. A study showed that adding Erbitux to standard chemotherapy increased survival by up to 21% in patients whose tumors carried a molecule called epidermal growth factor receptor.

**Gemzar for Pancreatic Cancer**
Only 5% of people with pancreatic cancer are still alive five years after their diagnosis. A large study of patients with early pancreatic cancer showed that, after surgery to remove their tumor, Gemzar chemotherapy doubled disease-free survival and increased overall survival.

**Treanda for Chronic Lymphocytic Leukemia**
In March 2008, the FDA approved Treanda for first-line treatment of chronic lymphocytic leukemia. An international study showed that Treanda completely eliminated cancer in 30% of Chronic Lymphocytic Leukemia patients.

**Avastin for Metastatic Breast Cancer**
Avastin has been used in colorectal and lung cancer. Last February, the FDA approved Avastin for use in combination with Taxol in patients with previously untreated metastatic breast cancer that does not carry the HER2 marker after a 2007 study showed that Avastin/Taxol combo doubled disease-free survival compared to Taxol alone.

**Long-Term Hormone Therapy for Breast Cancer**
To prevent breast cancer recurrence doctors used to give women five years of tamoxifen treatment. New studies showed that women can reduce their risk of breast cancer recurrence even more by taking tamoxifen or an aromatase inhibitor (such as Femara) for several years.

**Zometa for Breast Cancer**
Researchers last year learned that Zometa, a bone-strengthening drug, reduces the risk of breast cancer recurrence if given to premenopausal women undergoing hormonal-suppression therapy with tamoxifen or Arimidex plus Zoladex.

**Pegylated Interferon for Melanoma**
An European study showed that a year of treatment with pegylated interferon a newer, more active form of interferon, cuts the risk of recurrent melanoma by 18% in patients who had the deadly skin cancers surgically removed.

**Targeted Erbitux for Colon Cancer**
Studies showed that Erbitux only works in patients whose tumors carry a normal KRAS gene. This means that patients with KRAS-mutant tumors won’t benefit from Erbitux and will not unnecessarily suffer from side effects of the chemotherapy.

**The Pill Cuts Ovarian-Cancer Risk**
A review of data from 45 studies showed that for every five years they’re on the pill, women who take oral contraceptives cut their risk of ovarian cancer by 20%.

**HPV Vaccine May Cut Oral Cancers**
A 2008 study showed that oral cancers linked to human papillomavirus (HPV) went up in the US even though oral cancers not linked to HPV went down. That might be because of an increase in oral sex. If so, the HPV vaccine now approved for prevention of cervical cancer might have a role in preventing oral cancers, too.

**Oncologist Shortage Looms**
ASCO estimates that by the year 2020, the US will have 4,000 too few cancer specialists. By then, the number of cancer patients will increase by 55%. The number of oncologists is increasing at a much slower rate.

**Caring for Childhood Cancer Survivors**
One of the successes in the fight against cancer has been the increase in the number of kids who survive childhood cancer. A new study showed that 30 years after their cancer diagnosis, these kids are five to 10 times more likely than other kids to develop heart disease. The reason: side effects of cancer treatments. Their doctors must carefully monitor these survivors for heart problems and target them for prevention efforts.

For continued advances in cancer treatment and prevention, ASCO calls for increased federal spending on clinical cancer research and for removing barriers to participation in clinical trials of new cancer treatments.

*(WebMD Health News, Dec 15, 2008)*
CARCINOMA ESOPHAGUS:
AN OVERVIEW

Introduction

The esophagus is one of the common sites of malignancy in the gastro-intestinal tract. World over, the incidence of esophageal cancer, particularly adenocarcinoma, is on the rise. In the US, the incidence has increased five-fold. At the RGCI&RC, on an average 200 patients of cancer esophagus are registered every year. Unlike in the west, the majority of these are squamous cell carcinoma. The standard treatment of operable esophageal cancer in the absence of medical contraindications is surgery. Radiation, chemo-radiation for definitive treatment, and combination of radiation and chemotherapy with surgery are other treatment options. However, the overall survival continues to remain far from satisfactory. The reported five-year survival ranges from 5% to 30%.

Staging

Staging of cancer is important for uniform reporting and comparison of results from various centres. It also determines whether the intent of treatment is curative or palliative. It is based on clinical examination and information obtained by imaging: CT scan and/or endoscopic ultrasonography (EUS). TNM staging is one of the most important and reliable prognostic variables.

T-stage (Primary Tumour):
- TX: Primary tumour cannot be assessed
- T0: No evidence of primary tumour
- Tis: Carcinoma in situ
- T1: Tumour invades lamina propria or submucosa
- T2: Tumour invades muscularis propria
- T3: Tumour invades adventitia
- T4: Tumour invades adjacent structures

N-stage (Regional Lymph Nodes):
- NX: Regional lymph nodes cannot be assessed
- N0: Non-regional lymph node metastasis
- N1: Regional lymph node metastasis

M-stage (Distant Metastasis):
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

Tumours of the Mid thoracic Esophagus:
- M1a: Not applicable
- M1b: Nonregional lymph nodes and/or other distant metastasis

Tumours of the Upper Thoracic Esophagus:
- M1a: Metastasis in cervical nodes
- M1b: Other distant metastasis

For tumours of mid thoracic esophagus use only M1b, since these tumours with metastasis in non-regional lymph nodes have an equally poor prognosis as those with metastasis in other distant sites.

Investigations

Diagnostic Investigations: (1) Barium swallow is the first investigation in majority of patients presenting with dysphagia. It gives information regarding the site, length of lesion, morphology and extra esophageal spread. (2) Esophagoscopy is essential for biopsy/cytology.

Staging Investigations: (1) CT scan: Chest and upper abdomen. (2) Endoscopic ultrasonography (EUS). (3) Fiberoptic bronchoscopy: for tumours located at and above the level of the carina.

CT scan and EUS are complimentary for assessing the lateral extension of disease and lymph node status. EUS scores over CT scan in assessment of the depth of tumour invasion, particularly in early cancer and status of regional lymph node. However, in stricturous lesions, EUS may not always be possible. CT scan is equally accurate in assessment of T3/T4 lesions; abdominal CT scan additionally can screen liver and coeliac lymph nodes. Bronchoscopy is essential for assessing the tracheo-bronchial tree for early or frank invasion prior to surgery or radiation for upper and midesophageal disease. PET scan can effectively detect presence of disseminated disease. Thoracoscopy and laparoscopy for staging has reported increased rate of detecting positive lymph node metastatic disease.

Routine Investigations: Hemogram, Liver Function Test/Renal Function Test, Chest X-ray, Pulmonary Function Test and ECG.

Treatment Options

Performance status is important factor in determining the treatment of a patient with cancer esophagus. Patients with localized disease are ideally treated with surgery in the absence of medical contraindications. The preferred treatment of cervical esophagus is radical radiotherapy or concomitant chemo-radiotherapy.
Stage 0 (TisN0M0): The treatment of choice is surgery. If the disease is localised (preferably T1a), endoscopic mucosal resection (EMR) can be offered in centres with expertise, provided the patient is reliable for followup. For more extensive disease, esophagectomy is the treatment of choice.

Stage I (T1N0M0): Surgery is the treatment of choice. Radiation therapy may be offered if the patient is medically unfit or not willing for surgery.

Stage II/III (T2N0M0, T3N0M0, T1N1M0, T2N1M0): Surgery for T2 and T3 lesions. Surgery for T4 lesions with limited infiltration of pleura or pericardium which is amenable to complete resection. Neo adjuvant chemotherapy/concomitant chemo-radiation for T3/T4 tumours which are bulky or of doubtful resectability. If there is complete or partial response to neo adjuvant therapy and tumour appears resectable, the patient should proceed for surgery. If the response is sub-optimal and disease appears non-resectable, patient should either proceed for radiation or palliative therapy.

Investigational Treatments: (1) Chemo-radiotherapy alone or chemo-radiotherapy followed by surgery. (2) Neo adjuvant chemotherapy followed by surgery. (3) Post-operative radiation therapy.

Stage IVa (any T, any N, M1a): Surgery (primary or following neo adjuvant therapy) if the disease is operable in the absence of distant metastasis. However, more than 50% of patients will have distant metastasis. Such patients will be candidates for palliative treatment.

Surgical Approach: (1) Esophago-gastrectomy through left thoraco-abdominal approach (Garlock procedure): for adenocarcinoma of the cardio-esophageal junction. (2) Transthoracic esophagectomy with intrathoracic anastomosis (Ivor Lewis procedure). (3) Transthoracic total esophagectomy with cervical anastomosis. (4) Transhiatal esophagectomy with cervical anastomosis. Transthoracic esophagectomy has the advantage of mobilization of the esophagus under vision. Also, systematic mediastinal lymph node dissection can be performed. Transhiatal approach, according to proponents, is less morbid with fewer pulmonary complications. The majority of patients undergoing surgery have lymph node metastasis. Three-field lymph node dissection (lower cervical, mediastinal and abdominal) is reported to improve survival without increased procedure related morbidity and mortality. Carcinoma of the lower, mid and upper esophagus (excluding cervical esophagus) is managed either by transhiatal or transthoracic esophagectomy and esophago-gastric anastomosis in the neck or thorax.

New Developments: Two published (RTOG and ECOG) randomized trials have reported better overall survival (OS) with concomitant chemo-radiation than radiation therapy alone. Out of the three major trials comparing pre-operative concomitant chemo-radiation to surgery alone, one trial has shown statistically improved survival with chemo-radiation. Meta analysis of pre-operative chemo-radiation and surgery to surgery alone (nine trials) has reported improved 3-year survival and reducing loco-regional recurrence. Two major trials reporting dramatically opposite results have kept the issue of neo adjuvant chemotherapy controversial. In the absence of Level I evidence, post-operative radiotherapy is indicated only for patients with positive margin and residual disease. Phase 3 trials of surgery and post-operative chemotherapy have not reported survival benefit over surgery alone. In adenocarcinoma of the cardio esophageal junction, post-operative chemoradiotherapy is shown to improve the median OS.

Palliative Treatment

If the general condition is good: (1) Relief of dysphagia by placement of the esophageal stent alone, preferably self expanding metallic stent as these are easy to deploy. (2) Radiation therapy with intubation if associated with significant dysphagia. (3) Intraluminal radiation therapy alone. (4) Endoscopic laser destruction of tumour or electrocoagulation.

Treatment of esophageal fistula: (1) Esophageal intubation with stent. (2) Esophageal and tracheal/bronchial stent placement when possible if the fistula is large or if the tracheal lumen is compromised.

Conclusion

The incidence of esophagus cancer is rising. However, majority of the patients are still diagnosed in advanced stage of disease. The existing management approaches yield five-year survival between 5% and 30%. Hence, there is an urgent need for more multimodality management protocols to improve the existing dismal survival for patients with esophageal cancer. Specifically, the issue of neo adjuvant chemotherapy and concomitant chemoradiation needs to be addressed.

(The Institute appreciates Dr Rajesh Jain and Dr Kapil Kumar for their contributions to this feature on Carcinoma Esophagus: An Overview)
VIDEO-ASSISTED THORACIC SURGERY

Introduction

Technological advances during the 20th century have drastically revolutionized surgical practices and as a result, minimally invasive procedures have gained rapid diffusion. Thoracoscopy has changed a great deal since Jacobaeu first introduced the technique for the management of pleural effusion and tuberculosis in the early 1900s. It had almost been abandoned after the development of chemotherapy for patients with tuberculosis after 1950. It was only at the beginning of the 1990s with sensational advances in the technology and renewed interest towards minimally invasive surgeries that thoracoscopy was rediscovered. Video-Assisted Thoracic Surgery (VATS) is used to describe a modern minimally invasive surgical technique. VATS has developed very rapidly in the last two decades and has replaced conventional open thoracotomy as a standard procedure for some simple thoracic operations and as a complementary procedure for some other complex operations.

VATS

The structure of traditional thoracoscope is similar to other traditional endoscopes. It is a hollow tube with a simple light bulb over the tip of the scope with direct line of sight vision with distally lighted tubes. In VATS, the introduction of video-assisted imaging system amplifies the function of thoracoscopy. The minimal requirements of VATS include a zero and/or 30 degree rigid telescope(s), a light source and cable, a camera and an image processor. The introduction of video imaging technology and the wider availability of stapling devices facilitated an increasingly wider use of thoracoscopy for diagnostic and therapeutic purposes. VATS is principally employed in the management of pulmonary, mediastinal and pleural pathology. Interestingly, VATS is now becoming a useful adjunct in specialized orthopaedic and neurosurgical units for minimally invasive approaches to the spine; also, many of the procedures performed in adults are now described in the pediatric populations.

Indications

i) In pneumothorax-(a) spontaneous pneumothorax, (b) traumatic pneumothorax.
ii) VATS in chest trauma.
iii) In pulmonary benign or malignant diseases-(a) cancer diagnosis (visualization and biopsy including examination of solitary nodule), staging by mediastinoscopy; (b) minor lung resection (wedge resection); (c) major lung resection (lobectomy).
iv) In pleural effusion/empyema-(a) para-pneumonic effusion or empyema, (b) malignant pleural effusion.
v) In esophageal diseases—(a) esophagectomy, (b) anti-reflux surgery, (c) myotomy for achalasia.
vi) In mediastinal lesions—(a) VATS approach to thymus for myesthenia gravis and for thymoma; (b) VATS approach to posterior mediastinum for neurogenic tumors, mediastinal cysts, esophageal leiomyomata and paravertebral abcess.
vii) VATS in sympathectomy or splanchnicectomy.

Contraindications

Contraindications include patients with previous thoracotomies or with a history of extensive pleural disease, though not an absolute contraindication. Markedly unstable or shocked patients represent absolute contraindications. Other factors which make the thoroscopic approach difficult or impossible are obesity or increased thickness of the chest wall, narrow rib space, small chest or underlying conditions associated with increased bleeding.

Future Perspectives

VATS although widely applied has some difficulties for surgeons because of the loss of 3D vision, sense of touch and dexterity. Telepresence operation systems have been developed to solve these problems by increasing the dexterity, adding motion tracking and filtering tremor motions. Students can perform VAT surgery by using virtual reality surgical simulators instead of the real patients.

Conclusion

Most basic and many advanced thoracic surgical procedures can be performed by VATS with smaller wounds, less pain, shorter hospital stay and with as good outcomes as with conventional surgery. VATS is only a method instead of the goal of the treatment. Thus, conversion to open procedures should be done without hesitation if patient’s life safety is threatened or oncological principles are compromised.

(The Institute appreciates Dr Harit Chaturvedi and Dr Geeta Kadayaprath for their contributions to this Perspective on Video-Assisted Thoracic Surgery)
TOBACCO & CANCER

Introduction

Tobacco epidemic is man-made and totally preventable. It is one of the biggest public health threats which kills 5.4 million people a year (an average of one person every six seconds) and accounts for one in ten adult deaths worldwide. Unfortunately, the tobacco use is rising globally, especially in the developing world and the epidemic of its ill-health is still to peak. Tobacco causes lung and other cancers, heart disease, stroke and respiratory illnesses. Cigarette smoking causes 87 percent of lung cancer deaths and is responsible for most cancers of the larynx, oral cavity and pharynx, esophagus and stomach, bladder, kidney, pancreas, cervix and acute myeloid leukemia.

Tobacco Products & Risks

Tobacco products are made of tobacco leaf as raw material, which are intended to be smoked, sucked, chewed or snuffed. Tobacco is a slow killer and its damage to health becomes apparent years after onset of use. Cigarette smoke contains about 4,000 chemical agents, including over 60 carcinogens and many of these substances, such as carbon monoxide, tar, arsenic and lead that are poisonous and toxic to the human body.

Nicotine is a drug that is naturally present in the tobacco plant and is primarily responsible for a person’s addiction to tobacco products, including cigarettes. Nicotine is absorbed into the bloodstream and travels to the brain in a matter of seconds and also crosses the placenta and can be found in breast milk. Smoking harms nearly every major organ of the body. The risk of developing smoking-related diseases increases with total lifetime exposure to cigarette smoke. This includes the number of cigarettes a person smokes each day, the intensity of smoking (i.e. the size and frequency of puffs), the age at which smoking began, the number of years a person has smoked, and a smoker’s secondhand smoke exposure. Compared to never-smokers, smokers have about a 20-fold increase in lung cancer at present. Almost half of the world’s children breathe the air polluted by tobacco smoke.

WHO FCTC

World Health Organization Framework Convention for Tobacco Control (WHO FCTC) was developed in response to the globalization of the tobacco epidemic. It is an evidence-based treaty that reaffirms the right of all people to the highest standard of health. The core demand reduction provisions in the WHO FCTC are:

1. Price and tax measures to reduce the demand for tobacco
2. Non-price measures to reduce the demand for tobacco, namely:
   - Protection from exposure to tobacco smoke;
   - Regulation of the contents of tobacco products;
   - Regulation of tobacco products disclosures;
   - Packaging and labeling of tobacco products;
   - Education, communication, training and public awareness;
   - Tobacco advertising, promotion and sponsorship; and demand reduction measures concerning tobacco dependence and cessation.

WHO MPOWER Strategy

To reverse the devastating global tobacco epidemic, the WHO Tobacco Free Initiative programme emphasizes six key tobacco control measures known as WHO MPOWER Strategy that reflect and build on the WHO FCTC. These measures are:

1. Monitoring tobacco use and prevention
2. Protecting people from tobacco smoke
3. Offering help to quit tobacco use
4. Warning people about the dangers of tobacco
5. Enforcing bans on tobacco advertising, promotion and sponsorship
6. Raising taxes on tobacco

Tobacco Cessation

Tobacco cessation has major and immediate health benefits for men and women of all ages. The earlier a person quits, the greater the health benefit. The stoppage of use of tobacco products can stop or reverse most of the damage caused by it. Various nicotine replacement products can be used as switch over therapy. It is important to remember that there is no reason not to quit tobacco and it is never too late to quit. The community, particularly the health care providers, youth and women, should be educated and made aware about the relationship of tobacco use with cancer; and provided help and guidance by various support groups. Various tobacco control Acts have been legislated in India and abroad, though there are challenges in their implementation.

(The Institute appreciates Dr Abhey Sood for his contribution to the feature on Tobacco & Cancer)
BRCA 1 Influences Chemotherapy

According to Korean researchers, carriers of certain haplotypes of the BRCA1 gene, which plays a central role in the DNA repair system, do not appear to respond to platinum-based chemotherapy for non small cell lung cancer (NSCLC). Results from this study showed that lung cancer patients with two copies of AACC of BRCA1 do not benefit from platinum doublets-gemcitabine/platinum, docetaxel/platinum or paclitaxel/platinum - that are standard regimens worldwide for locally advanced or metastatic NSCLC. Researchers came to this conclusion after studying the relationship of 4 tagging single-nucleotide BRCA1 polymorphisms and their haplotypes on the outcome of treatment in 300 patients. The five haplotypes studied were AACC, AACA, GCTC, GATC and AATC. These patients had significantly shorter survival than those with one or no copy (8.7 versus 14.57 months). These results suggest that a new strategy is needed for these patients, especially in squamous cell carcinoma.

(J of Clinical Oncology, Dec 2, 2008)

Genes Linked to Lung Cancer Risk

According to the scientists from Fudan University, Shanghai, individuals with particular variants of certain genes involved in metabolizing the most potent carcinogen found in cigarette smoke have an increased risk of developing lung cancer. Tobacco specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a component of cigarette smoke that has been shown to cause lung cancer. ATP-binding cassette transporters encoded by genes known as ABCB1 and ABCC1 are involved in eliminating carcinogens from the lungs, protecting them against inhaled toxins.

The investigators found that patients who had the variant allele of either ABCB1 rs3842 or ABCC1 rs212090, had a significantly increased risk of developing lung cancer. The former variant was particularly associated with an increased risk of cancer in women and in individuals under age 60 years. It was also linked to a major type of lung cancer called adenocarcinoma. These findings have important implications for the prevention of tobacco smoking related cancers.

(Cancer, Feb 1, 2009)

Genetic Predictors of Esophageal Cancer

Researchers at M.D. Anderson Cancer Center have observed a significantly increased risk of esophageal cancer with increasing numbers of risk genotypes. They have identified 11 single-nucleotide polymorphisms (SNPs) in microRNA related genes that showed at least a borderline significant association with esophageal cancer. A person can have one or more of these SNPs in their genetic makeup, putting him or her into low-risk, medium risk and high-risk groups.

The study showed that each unfavorable genotype was associated with an increased cancer risk. Individuals with more than four unfavorable genotypes were more than three times as likely to develop esophageal cancer. Their ultimate goal is to construct a quantitative cancer risk prediction model based on an individual’s epidemiological profile, environment exposure and genetic makeup. This risk prediction model can evaluate each person’s relative risk and absolute risk of developing esophageal cancer within a certain time period. The majority of esophageal cancer patients are diagnosed at an advanced stage with poor prognosis. Understanding what places a person at high risk for esophageal cancer may have clinical applications to guide cancer screening, intensive monitoring and cancer prevention.

(J Cancer Prevention Research, Nov 2008)

Proton Therapy for Lung Cancer

Proton beam therapy is a specialized form of external beam therapy that uses protons rather than photons to kill fast growing cancer cells and is available in a few centers in the world. According to a study presented at the 2008 Chicago Multidisciplinary Symposium in Thoracic Oncology, sponsored by ASTRO, ASCO, IASLC and the University of Chicago, patients with locally advanced lung cancer who receive chemotherapy and proton therapy have fewer instances of a serious side effect called bone marrow toxicity than patients who receive chemotherapy, and another type of radiation therapy called intensity modulation radiation therapy. The findings suggest that using proton therapy over other types of radiation may allow doctors to give a higher dose of radiation without compromising the chemotherapy schedule to the lung tumor while avoiding bone marrow toxicity. These results are very promising and need to be confirmed with a randomized trial.

(Medical News Today, Nov 14, 2008)
NEW TECHNOLOGIES

CyberKnife® for Lung Cancer

CyberKnife Center of Palm Beach announced that it has enrolled the first patient in the landmark study comparing traditional surgery and CyberKnife® radiosurgery treatment outcomes in early stage operable and resectable lung cancer. The randomized, prospective clinical study led by the University of Texas MD Anderson Cancer Center will evaluate the potential for radiosurgery as a non-invasive treatment alternative for operable lung cancer patients. Though traditional surgery is the standard of care in the treatment of lung tumors, evidence over the past several years has shown excellent outcomes using high-dose precise irradiation delivered in three or four treatments. Data comparing the outcomes of surgery to less invasive treatment options, such as radiosurgery, are important to support clinical adoption of less invasive alternatives and potentially shift the treatment paradigm. This system continually tracks the tumor throughout the treatment to maximize targeting accuracy and minimize damage to the surrounding tissues and critical structures.

(Bio-Medicine, Dec 15, 2008)

Detection of Dysplasia and Cancer

To identify pre-neoplastic conditions, such as Barrett’s epithelium & dysplasia and evaluate the depth of penetration of early-stage esophageal neoplastic lesions, optical coherence tomography (OCT), an optical imaging modality, performs high resolution, cross-sectional, subsurface tomographic imaging of the microstructure of tissues. The physical principal of OCT is similar to that of B-mode ultrasound imaging, except that it uses infrared light waves rather than acoustic waves. The in-vivo resolution is 10-25 times better (about 10 mum) than with high-frequency ultrasound imaging. Esophagus and the esophago-gastric function have been the most widely investigated organ so far. OCT permits an accurate evaluation of mucosa, lamina propria, muscularis mucosa and part of submucosa. OCT imaging from the gastrointestinal tract can be done by using narrow-diameter, catheter-based probes that can be inserted through the accessory channel of either a conventional front view endoscope or a side view endoscope.

(World J Gastroenterol, Nov 14, 2008)

Localization of Pulmonary Nodules

Children with cancer may develop metastatic pulmonary nodules. Thoracotomy is considered the standard approach for resection of pulmonary nodules. Minimally invasive thoracoscopic ultrasound is a real time imaging tool that helps isolate small pulmonary lesions that may otherwise be difficult to see intraoperatively. Two 5-mm ports are inserted, one for the grasper and the other for the camera. One 12-mm port is inserted for the flexible 10-mm ultrasound probe and the endoscopic stapler. The patient has CO₂ insufflation to create a 5mm Hg pneumothorax. Twenty ml/ kg of normal saline is introduced into the chest cavity for acoustic coupling. The ultrasound probe is used to isolate the nodule(s), guide resection and check margins. Gow KW et al from the Emory University School of Medicine, Atlanta, USA, performed 8 procedures on 7 patients (median age - 15.2 years). Patients had primary diagnosis of osteosarcoma, wilms and lymphoma. They advocated this technique for those patients having video-assisted thoracoscopy to assist clarifying whether focal lesions are malignant, thereby guiding therapy.

(J Pediatr Surg, Dec 2008)

Nanotubes Detect Lung Cancer

Researchers at the Israel Institute of Technology have developed diagnostic system using an array of chemiresistive random network of single-walled carbon nanotubes coated with non-polymeric organic materials that show a high potential for diagnosis of lung cancer via breath samples. To calibrate the devices, the investigators captured the breath of 15 non-smoking healthy patients and 15 individuals with stage 4 lung cancer. They concentrated the organic compounds in each breath sample using solid phase micro-extraction and analyzed each sample using gas chromatography-mass spectrometry. The sensors array showed excellent discrimination between the volatile organic compounds (VOCs) found in the breath of patients with lung cancer, relative to healthy controls, especially if the sensors array is preceded with either water extractor and/or pre-concentrator of VOCs. The pattern compositions of the healthy and cancerous states were determined by gas-chromatography linked with mass spectroscopy analysis of real exhaled breath. The researchers are testing this system on a much larger group of patients and healthy subjects.

(NCI News, Nov 2008)
CLINICAL TRIALS

Gemzar® and Paraplatin® for SCLC

Small cell lung cancer (SCLC) often spreads quickly to distant sites in the body. The standard regimen for treating patients with SCLC is Platinol (cisplatin) and VePesid (etoposide).

According to a multicenter clinical trial in the United Kingdom, a combination of Gemzar® (gemcitabine) and Paraplatin® (carboplatin) is as effective as gold standard Platinol® and VePesid® for palliative treatment of patients with poor-risk SCLC in terms of overall survival and progression-free survival and has a toxicity profile more acceptable to patients. 241 patients with untreated, extensive SCLC were randomly assigned to receive six, three-weekly cycles of either Gemzar and Paraplatin or Platinol and VePesid. Although the outcomes from both regimens appeared to be equivalent, the group of patients receiving Gemzar/Paraplatin reported a higher quality of life. Nausea and hair loss were less frequent than in the Platinol/VePesid group. Although grade 3-4 myelosuppression was more frequent in the Gemzar/Paraplatin group, it was not associated with increased infection or fatalities. Patients tended to be able to tolerate more rounds of treatment.

(Thorax, Jan 2009)

New Indication for Tarceva

Tarceva (erlotinib) is a small molecule designed to target the epidermal growth factor receptor pathway, which is one of the factors critical to cell growth in non small cell lung cancer (NSCLC) and is currently approved as a second-line treatment for patients with advanced NSCLC. A Phase 3 study (SATURN) showed that Tarceva improved progression-free survival as a first-line maintenance therapy for advanced NSCLC. SATURN is a placebo-controlled, randomized, double-blind, Phase 3 study conducted by Roche that enrolled 889 patients with advanced NSCLC at approximately 160 sites worldwide. Patients were treated with at least four cycles of standard first-line platinum-based chemotherapy and were then randomized to tarceva or placebo, if their cancer did not progress. The primary endpoint of the study was progression-free survival. Genentech Inc, and OSI Pharmaceuticals Inc announced that SATURN met its primary endpoint and showed that tarceva significantly extended the time patients with advanced NSCLC lived, without their cancer getting worse when given immediately following initial treatment with platinum-based chemotherapy, compared to placebo.

(Medical News Today, Nov 8, 2008)

Non-platinum Regimen for NSCLC

A randomized, open-label, Phase 3 study conducted in Japan indicated that the non-platinum regimen of Navelbine® (vinorelbine) and Gemzar® (gemcitabine) followed by Taxotere® (docetaxel) appears to be as effective as the standard regimen of Paraplatin® (carboplatin) and Taxol® (paclitaxel), but with less toxicity, for patients with advanced non-small cell lung cancer (NSCLC). The study included 401 patients with Stage IIIIB or IV NSCLC who were randomized to receive one of the regimens. The experimental regimen was as effective as the standard regimen, indicating median overall survival of 13.6 months and 14.1 months, partial response of 25% and 37%, and median progression-free survival of 5.5 months, and 5.8 months, respectively. The toxicity profiles were different. Patients who received the standard regimen experienced more grade 3-4 neutropenia, central nervous system symptoms, and joint and muscle pain. Patients in the experimental group experienced more pulmonary toxicity.

(Lancet Oncology, Dec 2008)

Targeted Therapy for Lung Cancer

A Phase 3, multicenter, placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of bevacizumab (avastin) in combination with erlotinib (tarceva) compared with erlotinib alone for treatment of advanced non-small cell lung cancer after the failure of standard first-line chemotherapy, demonstrated a higher rate of tumor shrinkage and a longer interval before cancer progression, when bevacizumab was added to standard second-line erlotinib therapy. The study found that the addition of bevacizumab to erlotinib did not improve overall survival compared to erlotinib and placebo. However, there was clear evidence of clinical activity with improvements in progression-free survival and response rate when bevacizumab was added to erlotinib compared to erlotinib alone. Researchers at the Sarah Cannon Research Institute in Nashville were hopeful that the combination of the two agents that target different pathways would show a survival benefit.

(Science Daily, Nov 25, 2008)
Camptothecin for Cancer Treatment

United States Patent and Trademark Office has issued Patent No 7,462,627 to Enzon Pharmaceuticals Inc. (Bridgewater, NJ) entitled “Multi-arm polymeric conjugates of 7-ethyl-10-hydroxycamptothecin for treatment of lung, breast, colorectal, pancreatic and ovarian cancers.” Camptothecin is a water-insoluble cytotoxic alkaloid produced by camptotheca acuminate trees indigenous to China and nothapodytes foetida trees indigenous to India. It is a potential anticancer agent. Camptothecin and analogs are known as DNA topoisomerase I inhibitors. One of camptothecin analogs is Irinotecan (CPT-11, Camptosar. RTM). 7-ethyl-10-hydroxy camptothecin is an active metabolite of CPT-11. The present invention relates to multi-arm polymeric prodrugs of 7-ethyl-10-hydroxycamptothecin. In particular, the invention relates to four-arm polyethylene glycol conjugates of 7-ethyl-10-hydroxycamptothecin. Methods of making the conjugates and methods of treating mammals using the same are also disclosed.

(USPTO, Jan 5, 2009)

MicroRNAs’ Role in Lung Cancer

Micro RNAs (miRNAs) are a class of small, non-coding RNAs. Univ Ohio (US); Health and Human Services NIH have been assigned patent No. US2008306017 (A1), entitled “Microrna-Based Methods and Compositions for the Diagnosis, Prognosis and Treatment of Lung,” published on Dec 11, 2008. The present invention provides novel methods and compositions for the diagnosis, prognosis and treatment of lung cancer, based in part on the identification of specific miRNAs associated with altered expression levels in lung cancer cells. The level of at least one miR gene product in a test sample from the subject is compared to the level of a corresponding miR gene product in a control sample. An alteration in the level of the miR gene product in the test sample relative to the level of a corresponding miR gene product in a control sample, is indicative of the subject having or being at risk of developing lung cancer. The level of at least one miR gene product can be measured using quantitative or semi-quantitative RT-PCR, Northern blot analysis or solution hybridization detection.

(European Patent Office, Jan 7, 2009)

Modulators of c-Jun

European Patent Office has issued Patent No GB 2450180 (A) dated Dec 17, 2008 to Ferreira Pepa Ganchevska (GB) et al for “Treatment of lung cancer using modulators of c-Jun”. c-Jun is a major component of the AP-I transcriptional complex, which recognizes AP-I and CRE-like sites in gene promoters. c-Jun is necessary for cellular expression of ICAM, cycling DI and mdr1 genes, but the function of bcl-2 could be changed by c-Jun through the direct protein-protein interaction. c-Jun regulates cell cycle progression and apoptosis in epithelium lung cells. The present invention relates to the role of c-Jun transcription factor and AP-I transduction pathway in the pathogenesis of lung cancer and discloses therapeutic agents for the treatment of lung cancer that inhibit the activity or expression of c-Jun. The agents may affect the signaling pathway between c-Jun and mdr1, cyclinD1, bcl-2, ICAM-I or ERa. The present application also concerns a method of measuring the proliferative activity of lung cancer cells comprising testing the levels of c-Jun and ERa and for measuring chemotherapy resistance of lung cancer cells, comprising testing the levels of c-Jun, mdr1 and bcl-2.

(exp@cenet.com, Jan 12, 2009)

Nodule Detection

Medicsight PLC from Great Britain has been assigned United States Patent No 7,460,701 entitled “Nodule detection” on December 2, 2008. Detection of suspicious lesions in the early stages of lung cancer can be considered the most effective way to improve survival. The present invention relates to a method of detecting nodules in computed tomography (CT) images, and particularly but not exclusively for detecting nodules in CT images of the lung. The method may be implemented using a computer, and the invention encompasses software and apparatus for carrying out the method. A method of detecting a nodule in a three-dimensional scan image comprises calculating a three-dimensional sphericity index for each point in the scan image, applying a high sphericity threshold to the sphericity index to obtain a candidate nodule region, and then performing region-growing from the candidate region using a relaxed sphericity threshold to determine an extended region including less spherical parts connected to the candidate region. Optionally, spherical filtering may be applied to the image by matching the spherical filter to the extended region.
Lung Cancer Overtakes Breast Cancer

A new report from the Australian Institute of Health and Welfare reveals that lung cancer has overtaken breast cancer as the cause of most of the cancer deaths in Australian women. In 2005, more than 50 Australian women lost their battle with lung cancer every week; this figure is expected to rise to almost 65 female deaths per week in 2010. According to the Policy Manager at Quit, the number of lung cancer deaths was a legacy from higher female smoking rates in 1970s and 1980s. The number is not expected to decrease for some time. In the past, the tobacco industry targeted female smokers with advertising suggesting that smoking is glamorous or fashionable. Unfortunately, these active campaigns to recruit female smokers are now translating into higher lung cancer deaths. The figures released emphasized the importance of stepping up efforts to reduce the smoking rates and there is no doubt that a sustained commitment to tobacco control and mass media campaigns will lay the foundations to reduce the devastating toll of smoking.

(Australia: Cancer Council Victoria, Dec 19, 2008)

Tuberculosis and Lung Cancer

Tobacco and indoor air pollution from smoky coal are major causes of lung cancer in rural Xuanwei County in China. Tuberculosis has been suggested to increase lung cancer risk, but data from prior studies are limited. In a retrospective cohort study of 42,422 farmers in Xuanwei, interviewers administered a standardized questionnaire that included lifetime medical history, including tuberculosis. Tuberculosis was reported by 246 subjects and 2,459 died from lung cancer during follow-up. Lung cancer mortality was substantially higher in subjects with tuberculosis than in others. The association was especially pronounced in the first 5 years after tuberculosis diagnosis but remained strong 5-9.9 years and 10+ years after tuberculosis. These associations were similar among men and women and among smoky coal users. In Xuanwei, China, tuberculosis is an important risk factor for lung cancer. The increased lung cancer risk, persisting years after tuberculosis, could reflect the effects of chronic pulmonary inflammation and scarring arising from tuberculosis.

(China: Int J Cancer, Oct 1, 2008)

World Cancer Report 2008

The International Agency for Research on Cancer (IARC) at Lyon, France has announced the launch of the World Cancer Report 2008. The report highlights the growing global cancer crisis and emphasizes the need for a coordinated international approach. It provides the scientific basis for what should be undertaken and what could be achieved. The greatest impact of this increase in the global cancer burden will fall on the low and medium-resource countries. A major issue for many countries even among high-resource countries, will be how to find sufficient resources to treat all cancer patients effectively and provide palliative, supportive and terminal care of the large numbers of cancers which will be diagnosed in the coming years. The report provides a clear message of hope although cancer is a great and growing devastating disease. It is largely preventable and possibilities for prevention exist at present in all resource settings. Understanding of cancer is increasing and new approaches to therapy are being introduced. For identification of risk factors and mechanisms for cancer causation, prevention research needs to take on a higher profile and importance in cancer research strategies and in national cancer plans that are currently being developed.

(France: IARC News, Dec 19, 2008)

Smoking Rate Declines

The number of adult cigarette smokers in the US has declined for the first time in 4 years, according to a report released by the Centers for Disease Control and Prevention (CDC). The CDC reports that there were 43.4 million current smokers in the US (19.8%) in 2007, a one percent decline from the 20.8% in 2006. The findings were based on data from the 2007 National Health Interview Survey. These data reflect exceptional progress in the effort to reduce and eventually eliminate the death, disease and economic challenges that tobacco use brings on its users. Adult tobacco user prevalence is now under 20 percent for the first time since tobacco use rates began to fall during the mid 1960s. With tougher legislation and higher prices for cigarettes, smoking may be less attractive to more and more people. This year’s decline reflects the efforts in recent years to raise cigarette prices through higher taxation and to increase quit attempts (and to protect nonsmokers) through more widespread support for smoke-free environments, the effect of which may take several years to measure.

IN FOCUS

TUMOR BOARD

Introduction

Tumor Board is a multispecialty clinic or a forum for multidisciplinary consultations on diagnostic and treatment aspects of a cancer patient. It provides a mechanism for reaching a consensus on treatment through the empirical process of cross-exchange of opinions against one another and through facts. The mechanism follows democratic principles, that is, full and equal representation of all views. Tumor Boards are conducted in a wide spectrum of hospitals and institutions that vary in size and function. Tumor Boards or multispecialty clinics must be held in every oncology centre or oncology department of superspecialty hospital.

Tumor Boards provide a forum for pretreatment evaluation for resolving controversial management problems, estimating prognosis, staging for planning, post-treatment follow-up and considering rehabilitation and other supportive care.

Composition and Functioning

In an established institution, members of Tumor Board should include surgical oncologist, medical and radiation oncologists, pathologist, radiologist, administrator, social worker, oncology nurse, psychologist, occupational therapist and patient’s primary care physician. There must be a recognized leader with designated responsibilities to ensure the smooth functioning of the Tumor Board. In addition, there may be a facilitator or coordinator whose main responsibility should be to organize Board meetings.

1. Tumor Board Chairman/Chair to conduct the Board meeting.
2. Tumor Board coordinator or facilitator to act as ‘glue’ who ensures the continuity of Board meetings.
3. Dedicated meeting room with adequate facilities.
4. Interactive computer system, preferably picture archiving and communication system, video conferencing or teleconferencing equipment and Information Technology support.
5. Twice a week meeting of one hour duration is enough.

The case presentations follow a standard format. There is a concise description of the history and physical findings, pertinent pretreatment evaluation and staging, multidisciplinary discussion of the management options and final recommendations.

Challenges

1. Resource Constraints: (a) Time constraints, (b) Lack of specialists or coordinator, (c) Lack of IT support.
2. Financial Concerns: There is a need for financial compensation to encourage participation of all members.
3. Legal Concerns: Entry of conflicting views of members of board in case sheets.

Efficacy of Boards

These case discussions extend mostly beyond the patient care. They fortify knowledge, enrich experience and deepen our sympathy for the humane condition. Tumor Boards exert a unifying influence in medical practice because they bring together the different specialties in search of optimal treatment of a difficult disease. With its multidisciplinary representation, no group other than Tumor Board is better prepared to treat the patient who may feel fragmented by the treatment approaches offered by different medical specialties. Initial management decisions are often critical in determining the ultimate outcome.

Tumor Boards benefit the patients, clinicians, paramedical staff and the institution. It is estimated that a minimum of 60% of cancer patients stand to benefit from multidisciplinary treatment planning. Patients appreciate the concern shown by doctors when their condition is discussed at the Tumor Board meeting.

We at Rajiv Gandhi Cancer Institute & Research Centre conduct Tumor Boards thrice a week. We discuss cases of clinical interest, controversial issues and cases with diagnostic and therapeutic problems. On an average, 10 senior consultants and 20 residents participate in the discussions contributing at least 5000 man hours/year to better patient care. The hospital does not charge the patient for consultation for his/her case presentation at the Tumor Board. Management decisions made at the Tumor Board meeting avoid unnecessary diagnostic evaluation and reduce the cost of care.

In medicine, it is difficult to resist the pressure of experience as shared through the Tumor Board. When all the alternatives have been sifted, convergence of opinion becomes the accepted course of action.

What matters is our loyalty to our patient, not our hope of curing all cancers. We converse at the Tumor Board to make further conversations unnecessary.

(The Institute appreciates Dr A K Dewan for his contribution to ‘In Focus’ on Tumor Board)