International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (2): 1038-1045
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Biological Sciences | Open Access | MCI Approved
UGC Approved Journal

Small Cell Lung Carcinoma: An Updated Review

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Received: 20 Jan 2019 / Accepted: 22 Mar 2019 / Published online: 1 Apr 2019
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Abstract
Small cell lung carcinoma (SCLC) is a progressive deadly disease around the world. SCLC is a "small blue round cell tumor" originated from neuroendocrine cells. Small cell lung carcinoma accounts for about 15 percent of lung cancers. SCLC progress rapidly from larger airways (bronchi) of the lungs and often to the brain. It initially responds well to chemotherapy but unfortunately recurrance may occur after initial treatment and become more resistant to subsequent chemotherapy treatment. They are divided into only two stages, limited and extensive stage small cell lung cancer. SCLC is found most often in people with a history of tobacco use particularly smoking. SCLC is hallmarked by different abnormalities of many tumor suppressor genes. TP53 is mutated in 70-90% of SCLC cases. Similarly, the malignant tumor (Rb) cistron product is absent in a very overwhelming majority of cases. However, the overall cure and survival rates for SCLC remain low, particularly in metastatic disease. Therefore, continued research for the development of new drugs and combination therapies is required to expand the clinical benefit to a wider patient population and to improve outcome in SCLC.

Keywords
Small cell lung cancer, Screening, Prevention, Treatment.

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INTRODUCTION
Small cell lung carcinoma is also known as small cell cancer or oat-cell carcinoma. [2] Because to its clinical and biological characteristics small cell lung carcinoma (SCLC) is different from other lung cancer such as non-small cell lung carcinoma, mesothelioma and carcinoid cancers. SCLC is a highly malignant cancer that most mostly occures within the lung, even though it can occasionally arise in cervix, prostate and GIT.

SCLC could be a system cancer that features aggressive behavior, rise, early unfold to distinct sites, exquisite sensitivity to therapy and radiation, and perennial association with distinct paraneoplastic syndromes, including hypercalcemia, syndrome of inappropriate anti diuretic hormone (SIADH) secretion, and many others.

In patient with SCLC, it is important to determine whether the cancer is limited or at an extensive stage. In Limited stage cancer, combination of chemotherapy and radiation, with surgical resection

reserved for selected patients with stage I disease. Extensive stage cancer is untreatable; systemic chemotherapy is used to improve quality of life and prolong survival. [16]

PATHOPHYSIOLOGY

Small cell lung carcinoma (SCLC) ocures in peribronchial area and infiltrates the bronchial sub mucosa. Wide spread metastases occur early in the course of the disease, with common spread to the mediastinal lymph nodes, liver, bones, adrenal glands and brain.

In addition, production of various peptide hormones leads to wider range of paraneoplastic syndromes; the most common of these are the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) and the syndrome of ectopic adrenocorticotrophic hormone (ACTH) production. Additionally, auto immune phenomena may cause various neurologic syndromes, such as Lambert – Eaton syndrome.

Some of the pathological changes are: -

1. Small cells with scant cytoplasm
2. III-defined cell borders
3. Finely granular nuclear chromatin
4. Absent or inconspicuous nucleoli
5. Extensive necrosis

ETIOLOGY

The main cause of small cell lung cancer (SCLC) is tobacco smoking. Among all the types of lung cancer, SCLC and squamous cell carcinoma have the strongest connection to tobacco. Around the world approximately 95-98% of patients with SCLC have a smoking history. Patients with SCLC should be advised to quit smoking, because smoking cessation is associated with improved survival. All types of lung cancer occur with increased frequency in uranium miner, but SCLC is the most common. [39]. The small cell lung cancer may be caused due to the following:

- The main cause of both small cell lung cancer and non-cell lung cancer is tobacco smoking. However, small-cell lung cancer is more strongly correlate to smoking than non-small cell lung cancer.
- Second hand tobacco smoke is a major risk factor for lung cancer.
- Even all types of lung cancer occur with increased frequency in people who mine uranium, but small-cell lung cancer is most common. The prevalence is accrued any in persons United Nations agency smoke.
- It has been reported that Exposure to radon may cause small-cell lung cancer.
- Similarly, Exposure to asbestos greatly increases the risk of lung cancer. A combination of amphibole exposure and cigaret smoking will increase the chance of this disease.

EPIDEMIOLOGY

Lung cancer accounts for around 11-12% of all new cases of cancers worldwide, it is the second most common cancer in men and women, and it is the major cause of cancer-related death in the USA. SCLC represents 14% of all newly diagnosed cases of lung cancer worldwide, or more than 180000-190 000 cases per year. More than 91% of patients with SCLC are elderly current or past heavy smokers, and risk rises with increasing duration and intensity of smoking. Although rare cases have been reported in people who have never smoked, SCLC, by contrast with non-small cell lung cancer (NSCLC), is not associated with a specific somatic mutation. In industrialized countries the annual incidence of SCLC has decreased over the past 30 years, probably owing to changes in smoking patterns. A shift in the WHO classification of lung cancers might also have contributed, as some borderline cases that were previously described as mixed subtypes are now classified as NSCLC. An increase in incidence is expected in countries where smoking prevalence remains high, such as those in Eastern Europe and Asia. [10]

SCREENING AND DIAGNOSIS OF LUNG CANCER

Screening for Lung Cancer

Screening is carried out to detect a disease in patients who do not have symptoms of the disease. Three tests have been studied for use as screening tests for lung cancer. They are

1. **Chest X-ray**: It involves X-ray of the organs and bones inside the chest.
2. **Sputum cytology**: This is a process where a sample of sputum is viewed under a microscope by a pathologist to look for cancer cells.
3. **Low-dose spiral/ helical CT scan**: This test involves a CT scan with low-dose radiation to make a series of detailed pictures of the organs inside the body. Among these three tests, chest X-ray and sputum cytology have been found to have a low sensitivity for detection of lung cancer. [47]

DIAGNOSIS OF LUNG CANCER

If anyone has one or more symptoms indicative of lung cancer, he or she should visit the doctor, who will examine the patient and ask for relevant tests.

Imaging Tests:

- **Chest X-ray**: In this technique usually the doctor will get done to look for a mass in the lungs. If an abnormality is seen in the X-ray, further tests will be ordered.
- **Computed tomography (CT) scan**: A CT (or CAT) scan is more likely to show lung masses than X-ray. CT scans can also provide necessary information about the size, shape and position of lung tumors and help to find the spreading of the cancer to lymph nodes or other organs.
- **CT-guided needle biopsy**: If a suspicious mass is seen in the lung during CT scan, the doctor may perform a guided biopsy to take some tissue for diagnosis.
- **Magnetic resonance imaging (MRI) scan**: This technique is mostly often used to look for spread of lung cancer to brain and spinal cord to help in staging of the cancer.
- **Positron emission tomography (PET) scan**: A PET scan is very useful to see if the cancer has spread to lymph nodes or other areas. This technique determines whether surgery can be done or not. [17]

Laboratory Tests:

Imaging techniques are helpful for detecting a mass in the lung, but the actual diagnosis of lung cancer can be made by looking at the cells under a microscope.

- **Sputum Cytology**: A sample of sputum is viewed under a microscope to look for cancer cells. For this, there is a best method to submit early morning sputum samples obtained after a deep cough for 3 days in a row.
- **Needle biopsy**: This technique involves the insertion of a hollow needle into the mass to get a small sample for testing. This can be done by fine needle aspiration biopsy (FNAB). [26]
- **Bronchoscopy**: For this test, a flexible fiber-optic tube (bronchoscope) is passed through the mouth or through the nose and down into the windpipe and further.
- **Thoracentesis**: This procedure is performed if there is a build-up of fluid around the lungs (pleural effusion), which can cause difficulty in breathing. Effusion cytology is a process in which a hollow needle is inserted between the ribs to drain the fluid and check for tumor cells in the fluid. [3]

MANAGMENT OF SCLC

Treatments for SCLC can include: -

- Chemotheraphy for SCLC
- Immunotheraphy for SCLC
- Radiation theraphy for SCLC
- Surgery for SCLC
- Palliative proceures for SCLC

❖ **Chemotherapy for Small Cell Lung Cancer: -**

This technique involves the treatment with anti-cancer drugs injected into a vein or taken by mouth. These drugs enter the bloods and go throughout the body, making this process useful for cancer anywhere in the body. [21]

Drugs used to treat SCLC

SCLC is treated with combinations of chemotherapy drugs. The combinations most often used are:

- Cisplatin and etoposide
- Carboplatin and etoposide
- Cisplatin and irinotecan
- Carboplatin and irinotecan

❖ **Immunotherapy for Small Cell Lung Cancer: -**

Immunotherapy mainly refers to medicines that stimulate a person's own immune system to recognize and destroy cancer cells more effectively.

Immune checkpoint inhibitors

A most important part of the immune system is its ability to keep itself from attacking normal cells in the body. For this, it uses "checkpoints", which are proteins on immune cells that need to be turned on (or off) to start an immune response.

Nivolumab (Opdivo)

Nivolumab (Opdivo) is a very useful drug that targets PD-1, a protein on T cells (a specific type of immune system cell) that normally help to keep these cells from attacking other cells in the body. By blocking PD-1, this drug increases the immune response against small cell lung cancer cells. This can often shrink tumors. [7]

❖ **Radiation Therapy for Small Cell Lung Cancer: -**

Radiation therapy involves high-energy rays (such as x-rays) or particles to kill cancer cells.

Types of radiation therapy: -

Radiation therapy most often used for the treatment of SCLC is called external beam radiation therapy (EBRT). It delivers radiation mainly from outside the body and focuses it on the cancer. [53]

Three-dimensional conformal radiation therapy (3D-CRT): 3D-CRT uses special computer programs to precisely map the location of the tumor. Radiation beams are shaped and focused at the tumor (s) from several directions, which makes it less likely to damage normal tissues.

Intensity modulated radiation therapy (IMRT): It is an advanced form of 3D therapy. This technique uses a computer-driven machine which moves around the patient as it delivers radiation. Along with shaping the beams and aiming them at the tumor from several angles, the intensity of the beams can be adjusted to limit the dose reaching nearby normal tissues. [43]

❖ **Surgery for small cell lung carcinoma**

It has been rarely used as part of the main treatment for small cell lung cancer (SCLC), as the cancer has usually already spread by the time it is found.

Types of lung surgery

Different operations can be used to treat SCLC:

- **Pneumonectomy:** In this surgery an entire lung is removed.
- **Lobectomy:** Human lungs have 5 lobes. In this surgery, the entire lobe containing the tumor is removed.
- **Segmentectomy or wedge resection:** In this case, only the part of the lobe with the tumor is removed.
- **Sleeve resection:** in this process a section of a large airway is removed, and the lung is reattached. [42]

❖ **Palliative Procedures for Small Cell Lung Cancer**

Palliative, or supportive care, is focused to relieving symptoms and improving a person's quality of life. [20]

Treating an airway blocked by a tumor

Pneumonia or shortness of breath may be caused by growth of tumors into the lung airways and blocking them. Sometimes this is treated with radiation therapy but other techniques can also be used.

Photodynamic therapy (PDT)

Sometimes Photodynamic therapy is used to help open up airways blocked by tumors to help people breathe better.

For this technique, porfimer sodium is injected into a vein.

Laser Therapy

Laser therapy can sometimes be used to help open up airways blocked by tumors to help people breathe better.

The patients are usually asleep for this type of treatment. In laser therapy, one the end of a bronchoscope, which is passed down the throat and next to the tumor. The doctor then aims the laser beam at the tumor to burn it away. [51]

Stent Placement

Sometimes lung tumor has grown into an airway and is causing problems and this case a bronchoscope is used to put a hard silicone or metal tube called a stent in the airway to help keep it open. This is often done after other treatments such as PDT or laser therapy.

Treatment of fluid buildup in the area around the lung

In pleural effusion fluid can build up in the chest outside of the lungs. It can press on the lungs and cause trouble breathing. [19]

Thoracentesis

This is done to drain the fluid. For this procedure, the doctor will numb an area in the chest, and then place a hollow needle into the space between the lungs and the ribs to drain the fluid. Sometimes this is done using ultrasound to guide the needle into the fluid.

Pleurodesis

This procedure is used to remove the fluid and keep it from coming back. One way to do this is to make a small cut in the skin of chest wall, and place a hollow tube into the chest to remove the fluid. Then a substance is placed into the chest through the tube that causes the linings of the lung and chest wall to stick together, sealing the space and limiting further fluid build-up.

Catheter placement

Catheter placement is used to control the buildup of fluid. One end of the catheter is placed in the chest through a small cut in the skin, and the other end is left outside the body. [34]

Treating fluid buildup around the heart

Sometimes lung cancer can spread to the area around the heart. It can lead to fluid build-up inside the sac around the heart which can press on the heart and affect how well it works.

Pericardiocentesis

In this technique, the fluid is drained with a needle placed into the space around the heart. This is generally done using an echocardiogram to guide the needle.

Creating a pericardial window

It can be done to keep the fluid from building up again. In the surgery, a piece of the sac around the heart (the pericardium) is removed to allow the fluid to drain into the chest or belly.

Some drugs approved for small cell lung carcinoma

- **Afnitor(Everolimus)**

US Brand Names: -

Afinitor

Afinitor Disperz

Zortress

FDA Approved: Yes

Use in Cancer: -

Everolimus is used to treat: -

1. Renal cell carcinoma
2. Breast cancer

3. Pancreatic cancer, gastoinstestinal cancer & lung cancer.
4. Subependymal giant cell astrocytoma.

- **Doxorubicin Hydrochloride**

FDA Approved: Yes
Use in Cancer: -
Doxorubicin hydrochloride is used for the treatment of
1. Acute lymphoblastic
2. Acute myeloid leukemia(AML)
1. Breast cancer
2. Neuroblastoma
3. Thyroid cancer
4. Gastric cancer
5. Ovarian cancer
6. Soft tissue and bone sarcomas

- **Etopophos(etoposide Phosphate)**

US Brand Names
Etopophos
FDA Approved: Yes
Use in cancer: -
Etoposide phpsphate is approved to be used with other drugs to treat: -
1. Small cell lung cancer
2. Testicular cancer

- **Hycamtin(Topotecan Hydrochloride)**

US Brand Names
Hycamtin
FDA approved: Yes
Use in Cancer: -
Topotecan hydrochloride is used for the treatment of
1. Cervical cancer
2. Ovarian cancer
3. Small cell lung cancer

- **Mechlorethamine Hydrochloride**

US Brand Names
Mustargen
FDA Approved: Yes
Use in Cancer: -
Used for the treatment of: -
1. Bronchogenic carcinoma
2. Chronic lymphocytic leukemia (CLL)
3. Chronic myelogenous leukemia (CML)
4. Hodgkin lymphoma
5. Malignant pleural effusion

- **Methotrexate**

US Brand Names
Rheumatrex
Trexall
FDA Approved: Yes
Use in Cancer: -
1. Acute lymphoblastic leukemia
2. Breast Cancer
3. Lung cancer
4. Mycosis fungoides
5. Head and neck cancer
6. Gestational trophoblastic disease
7. Osteosarcoma
8. Non-Hodgkin lymphoma

- **Nivolumab**

US Brand Names
Opdivo
Opdivo injection
FDA Approved: Yes
Use in Cancer: -
Nivolumab is approved to be used for the treatment of
1. Colorectal cancer
2. Melanoma
3. Classical Hodgkin lymphoma
4. Hepatocellular carcinoma
5. Renal cell carcinoma

PREVENTION

For the prevention of lung cancer there is no proven way, but there are steps to lower the risk of getting lung cancer. One can help lower the risk of getting lung cancer in the following ways:

1. Avoid Smoking: The best way to prevent lung cancer is to not smoke. People who have never smoked have the lowest risk of lung cancer. Talk to the children about harmful effects of smoking so that they know how to face peer pressure and do not start smoking.

2. Quitting Smoking: However long anyone have been smoking, it is always worthwhile to quit smoking.

3. Avoid second hand smoke: If any one live or work with someone who smokes, urge him/ her to quit. If not, request them to smoke outside. It should be better to avoid smoking zones in public places like restaurants and bars.

4. Lower your exposure to radon: If any one live in an area where radon is a known problem, get the radon levels in their house checked and take measures to reduce exposure.

5. Lower exposure to workplace risk factors: Always Follow employers' precautions to protect from toxic chemicals at work.

The following help in reducing the risk of cancer in general, not specifically for lung cancer:

• Diet rich in fruits and vegetables
• Regular physical activity

CONCLUSION

SCLC remains a frustrating disease to research and to treat. In extensive-stage disease new drug combinations and approaches have made little difference to overall survival. Improved survival remains the ultimate goal as, unlike in other chemo sensitive cancers, second-line treatment is not an option for most patients.

Although most patients with limited-stage SCLC will also succumb, long-term survival has been improved by good integration of chemotherapy with early, accelerated chest radiotherapy and prophylactic cranial irradiation. A small proportion of patients with SCLC survive long term. The risk of death from the initial disease begins to decrease after 2 years. The risk of a second primary cancer, however, is 2–10% per patient per year, which is higher than in adult male smokers who have never developed lung cancer. Patients should, therefore, be monitored and refrain from smoking for life.

Etoposide and cisplatin remain the mainstays of first line SCLC treatment. Further investment in research for this disease is, therefore, warranted. Many phase 1 and 2 studies of drugs with potential activity in SCLC and phase 2 and 3 trials to improve radiotherapy are underway. Inclusion of patients with SCLC in such trials should be encouraged, especially otherwise healthy patients with relapsing or refractory SCLC, for whom treatment options are limited. A new, effective, and active combination for extensive-stage SCLC would be quickly moved up as a treatment priority.

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