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Review Article

ROLE OF INTEGRATIVE APPROACH IN THE PREVENTION AND TREATMENT OF LUNG CANCER WITH LATEST ADVANCES

Devang Sharma[1], Girija Kumari*[1], Vikram Singh[2]

[1]*Department of Clinical Research, Amity Medical School, Amity University Haryana, Gurugram, India*

[2]*Department of Medical Laboratory Technology, Amity Medical School, Amity University Haryana, Gurugram, India*

**Corresponding author: girijabiotech@gmail.com*

ABSTRACT

Lung cancer is the most common type of cancer leading to mortality worldwide. The 5-year survival rate of lung cancer patients is less than 18%. Much progress has been made in the past few years to fight with lung cancer. Various treatments and therapies such as surgery, radiotherapy, immunotherapy, targeted therapy, and chemotherapy are being used to benefit the patients suffering from lung cancer. The healthcare sector has evolved a lot in the past few decades. Once cancer is diagnosed, depending on the stage of cancer the patient can get the most suitable treatment ranging from chemotherapy to targeted therapy to surgery. Researchers have made biomarker testing possible now. It is possible now to find out the specific mutated genes that are causing the lung cancer, followed by providing the targeted therapy to the patient to treat cancer. This paper is designed to review the role of integrative and advanced approaches in the treatment of lung cancer.

Keywords: Lung cancer; Chemotherapy; Immunotherapy; Targeted therapy; Radiotherapy.

1. INTRODUCTION

At the present time the cancer is the foremost health problems around the world. Cancer is the second most common cause of death worldwide followed by cardiovascular diseases [1]. The lung cancer is the most common cause of death for both men and women worldwide. The death rate of lung cancer exceeds that of the three most common cancers (colon, breast, and pancreatic) combined [2]. Over half of patients diagnosed with lung cancer die within one year of diagnosis and the 5-year survival is around 17.8% [3]. Lung cancer became the most common type of cancer that is causing deaths worldwide. 2 million new cases of lung cancer were observed in 2018 [4].

Lung cancer is a disease which invades the lung tissue by formation of uncontrolled cell growth, and this may also affect the tissues near the lung (Metastasis). There are two main types of lung cancers, *i.e.* Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). Out of all types of lung cancers, 80% to 85% of lung cancers are NSCLC. All the subtypes of NSCLC including adenocarcinoma, squamous cell carcinoma and large cell carcinoma are grouped together as NSCLC [5]. The rate of growth and spread of SCLC is higher than that of NSCLC. Cancer is the condition of the uncontrolled growth of cells in the body. These cells undergo uncontrolled division and form a cluster of cells called 'tumor'. When the tumor detaches from its primary site of origin and starts moving to other body parts through blood and lymph then this movement of the tumor are called metastasis or metastatic spread.

A tumor can be originated in any body part such as lungs, prostate, skin, stomach, breath, brain, colorectal, and many more. A tumor cell if diagnosed at the early stage can be treated with various therapies such as immunotherapy, chemotherapy, radiotherapy, and with medication too. The cancer is of two types on the basis of the mobility of tumor, benign and malignant. Benign tumors stay localized and are small, slow-growing, non-invasive, and well-differentiated. Malignant tumors can metastasize and are large, fast-growing, invasive, and poorly differentiated [6]. Being the second most common cause of death around the world, according to WHO, cancer took about 9.6 million lives in 2018. Lung cancer in men and breast cancer in women are the most common types of cancer. About 1,806,590 new cases and 606,520 deaths due to cancer are estimated in the United States of America [7]. In India, the mortality rate due to cancer is extreme, i.e. 0.3 million deaths/year [8]. A report was published by ICMR on

Time Trends in Cancer Indices Rates. According to this report, a raise is observed in the cases of cancer in a time interval from 2010 -2020. According to the data, the cancer cases in 2020 will raise up to 1,148,757 from 979,786 in 2010. Tobacco relates cancer such as lung cancer and mouth cancer are supposed to rise from 190,244 in 2010 to 225,241 in 2020. Breast cancer alone is estimated to go beyond 100.000 by the year 2020 [9]. The main cause of cancer is still unknown to scientists and researchers, but there are many risk factors that can lead to uncontrolled cell division in the body. Tobacco, urban air pollution, indoor smoke of cooking and heating and radon in buildings are some of the major causes of cancer in the lungs, trachea, bronchus, stomach, and mouth worldwide. Currently there are many advanced therapies to treat cancer such as surveillance, radiotherapy, and chemotherapy, but there are chances that these therapies affect the patient negatively. The patient may face anxiety related to the risk of reoccurrence, overtreatment, second malignancy risk, cardio toxicity, and fertile impairment [10]. In the view of above this review will give the new insight of integrative and advanced approaches in the treatment of lung cancer.

2. SEARCH METHODOLOGY

We conducted a literature search of peer-reviewed original studies published worldwide from 2013-2020 in the English language as per as our study eligibility criteria. The search for review of literature based on cancer statistics, Integrative, complementary and advanced treatment for lung cancer, epidemiology of lung cancer, complications in lung cancer, and other treatment options treatment for lung cancer, prevention and management of cancer were searched through reputed databases including Pub Med Central, Google Scholar, Medline, EMBASE and Research Gate.

2.1. Current and integrative treatment for lung cancer

2.1.1. Surgery

The most commonly used surgical procedure is Video-Assisted Thoracoscopy Surgery (VATS). Patients of stages I, II, and IIIA NSCLC can undergo the VATS. In the VATS process, a small incision is made in the chest, near the lungs and a thoracoscope is inserted. The tumor or lobe is then removed by this scope. After surgery, patients are also sometimes provided with radiotherapy, chemotherapy, and targeted therapy. Providing these therapies helps to kill the cancer cell if remaining. The most common procedure for surgery is a lobectomy, in which the right and left lungs are divided into 3 and 2 lobes respectively. The lobe of the lung that is affected by cancer is then removed through surgery. Other procedures that are followed in surgery are Segmentectomy, Wedge resection, Pneumonectomy. There are several side effects such as pain, fatigue, cough, blood clots, and heart problems that the patient may face after undergoing surgery [11].

2.1.2. Adjuvant

The lung cancer patients who have a resection surgery take advantage from the adjuvant therapy to reduce the risk of lung cancer relapse. This adjuvant therapy may include targeted therapy, radiation,and chemotherapy. Lung cancer patient with stages IIA, IIB, and IIIA NSCLC generally take delivery of chemotherapy after getting surgery to destroy any residual cancer cells in order to make longer survival [12].

2.1.3. Radiotherapy

In this treatment high energy X-rays are used to shrink the tumor and to stop it from metastasizing. These methods are used as a primary treatment before and after the patients have undergone surgery. Before the surgery radiotherapy shrinks the tumors and destroys the rapidly multiplying cells. After the surgery, radiotherapy helps in killing the remaining cancer cells that may remain in the body.

Hiroshi Onishi [13] with her colleagues researched to see that are the results of Stereotactic Body Radiotherapy (SBRT) for stage I non-small cell lung cancer are comparable to surgery. Patients having no requirement of surgery or those who are not medically eligible for surgery are provided with SBRT. SBRT is also known as the cyber knife as it cuts down the localized tumor in the particular body organ. In SBRT treatment a high focused multitude of the radiation beam is passed through the lungs tracking the tumor cells. SBRT is mostly used in the initial stages of lung cancer. The study of Hiroshi Onishi proved that the SBRT treatment is safe and promising and the survival rates of patients undergone SBRT are comparable with that of surgery [13]. Apart from offering promising results, radiotherapy can cause some side effects to the patients. The side effects can include fatigue after the therapy, hair loss in the area of radiation field, skin irritation and inflammation, loss of appetite, and radiation pneumonitis [14].

2.1.4. Chemotherapy

Chemotherapy is a treatment that can be provided in all stages of cancer. In chemotherapy drugs that are toxic for tumor cells are injected in the veins of patients. These drugs decrease the speed of tumor cell division. Chemotherapy is also given in combination with radiotherapy to enhance the damage to toxic tumor cells in the body. Chemotherapy decreases the damage done by the tumor cells and stabilizes the tumor cells at a stage where they are more susceptible to radiotherapy. Hung MS conducted a study with their colleagues to know about the effect of giving radiotherapy along and giving with a combination of chemotherapy. The study showed that the 2-year survival rate of patients given both chemotherapy and radiotherapy was much higher than those who are given radiotherapy alone. The distant metastasis rate was also lower in the patients provided with a combination of both the therapies [15].

2.1.5. Immunotherapy

Immunotherapy is a type of biological therapy that let your immune system fight with cancer and tumor cells. Immunotherapy helps your immune system in recognizing and then killing the tumor cells. Tumor cells sometimes manipulate their characteristics due to which the immune system fails in recognizing them. Somasundaram [16] conducted a study and he found two checkpoint proteins, i.e. PD-L1 and PD-1. PD-L1 checkpoint protein is present on the healthy and normal tissue. PD-1 protein is present generally on T-cells, a type of white blood cells. In some cases, the tumor cells manipulate the immune system and start producing PD-L1 checkpoint protein on their own and get attached to the PD-1 checkpoint protein of T-cells. This manipulation makes the immune system disable to recognize the tumor cells as they also have developed the PD-L1 checkpoint protein similar to healthy and normal cells. The study shows the immunotherapy to be very helpful in such conditions. The immunotherapy, enhances the immune system and helps the immune cell to get attached either to the PD-L1 on the healthy and normal cells or the PD-1 on the T-cell. As the immune cells get attached to one of the checkpoints it stops the tumor cells from binding to the checkpoint proteins. After this change, the immune system can now easily attack the tumor cells [16].

2.1.6. Biomarker testing

Gene mutation can cause uncontrolled growth in the cell. Mutated genes are called biomarkers. Personalized medicines for these biomarkers are proven helpful in improving the survival rate of patients having NSCLC. To detect these mutated genes or biomarkers a small biopsy is done by pulmonologist or surgeon and the sample is examined by a pathologist. The pathologist classifies the cells by histology. Currently targeted therapy for lung cancer is only approved for advanced-stage cancer. Some several mutated genes or biomarkers are linked to lung cancer such as EGFR, ALK, BRAF, and KRAS. Based on the type of biomarker detected, the physician can prescribe you a medication that is approved to treat tumors linked with that specific biomarker [17].

2.1.7. Tumor cell vaccines

Belagenpumatucel-L is the genetically engineered entire tumor cell allogene vaccine. This consists of 4 radiated gene-modified NSCLC lines (TGF-β2, 2 of which are adenocarcinoma lines), 1 is a squame line, and one is a widespread cell carcinoma line respectively, H 520, SKLU-1 and RH2. Higher (TGF)-β2 rates are correlated with immune system suppression contributing to the neutralization of cells that damage normal cells and dendritic cell suppression [18, 19].

Belagenpumatucel-L has another function to perform in its immune stimulation Impacts on NSCLC cells by activating a certain T cell reaction. The vaccine will suppress tumour-production by its specific antisense RNA, the plasmid (TGF-β2) transgenic component [20].

2.1.8. Liposome BLP25 vaccine

A peptide-based vaccine, which attacks the uncovered core peptide of membrane-associated glycoprotein (MUC1), is widespread in most respiratory, genetic and digestive cell apical surfaces. Liposomal BLP25 is the most widely identified petrotein-associated glycoprotein vaccine. When MUC1 becomes glycosylated aberrantly, in regular cells it is resistant to MUC1. Over expression of MUC1 is linked to about 60% of lungenary cancer and also to higher immunosuppression and a less severe diagnosis in patients with MUC1 andenocarcinoma [21]. In a randomized Step IIb trial, the safety and Toxicity consequences of the L-BLP25 vaccine have been tested in patients with stage IIIB and IV NSCLC. L-BLP25 plus best-supporting treatment (BSC) and BSC single-group patients have been randomized in groups of 88 to 83 patients respectively. L-BLP25 and BSC patients Community had an overall 4.4-month recovery period compared with BSC alone patients [22].

2.1.9. Radical radiotherapy

Radiotherapy is continuing to evolve and various techniques are currently being used for curative treatment of lung cancer. In the early 2000s, however, stereotoctic ablative radiation (SABR) has not been widely used since late 2000 in the UK and has been developed for use in lung cancer and has been able to provide large doses of high-precision 1–2 mm radiation to a minor lesion of <1 cm^3 with the use of an external 3D coordinated system that is linked to movements in the air cycle.It is primarily intended for early-stage cancer patients that have not necessarily been operated on owing to existing co-morbidities. A meta-analysis of retrospective research found that SABR has an edge in survival over traditional radiation purpose (2-year survival 70 percent) [23]. A prospective Phase II cohort study also found that 3-year survival in T1–2 N0 M0 lung cancers was 55.8 percent with SABR(24). SABR has higher local disease prevention outcomes than traditional radiotherapy at 3 years as well as increased average survival (87.2% SABR vs. Classic radiotherapy 43 percent) [24, 25].

2.1.10. Radiofrequency / microwave ablation

Percutaneous radiofrequency ablation (RFA), initially used for the treatment of primary or secondary hepatic tumors, was first described by Dupuy*et al.* in 2000 (26). This is seen in patients with potentially inoperable early stage residual lung tumor or metastasis. In the CT instruction, a multi-electrode expandable needle is percutaneously mounted. Then the electrons induce thermal death of the cells and clot necrosis to travel through a sinusoidal current. Alternatively, the same ablative result may be accomplished with a microwave sample. Pneumothorax is the most frequent condition identified but only 4–16% of the patients need installation of chest drains [27]. No reports comparing RFA results with surgical resection, but 75 percent in stage I inoperative lung cancer overall survival was recorded in cases collection [28].

2.1.11. Supportive and palliative care

Palliative care professionals play a significant part in managing lung cancer and a lot has been achieved to maximize the application of lung cancer and enhance the outcomes of patients. In contrast to routine care of ambulatory patients with NSCLC-metastatic referred to a specific department of medical oncology, Temel *et al.* investigated the impact of early palliatory diagnosis [29]. The mean longevity of the early intervention community, 11.6 months, had a substantial variance comparison with the regular treatment category, 8.9 months.The standard of life for these people was therefore increased and their conditions became less stressful, so violent end-of - life treatment became less possible. The finding is supported by an additional study, in which patients receiving early care have improved their 1 year survival [30].

2.1.12. Complementary and alternative medicine

Modern surgical treatments are costly and related to unnecessary toxicity. The definition of Complementary and alternative medicine (CAM) includes whole medical systems – as in India and China, Ayurveda, homoeopathy, naturopathy and traditional Chinese medicine, are used as a major medical practice. Patients are also allowed for non-conventional treatments such as compliant and alternative (MATs). Current terminology is commonly used in complementary (conjoint medicine therapies used), alternative (conventional medicine instead of therapy) and integrative (evidence-based CAM practice with conventional medicines used) medicine [31].

In 1998, the National Institute of Health (NIH) established the National Center for Complementary and Alternative Medicine (NCCAM) to investigate approaches generally not considered part of traditional medicine, and expanded public interest, as well as requests from population, medical practitioners, media and government agencies. This CAM approach consists of five types of treatments (a)complete medical systems (Allopathic, Ayurvedic, homeopathy, Chinese traditional medicine, and naturopathy),(b) mind–body medicine which may include yoga, meditation, cognitive therapy, healing touch, relaxation, visualization/imagery, aromatherapy, dance, hypnosis, music, art, prayer, sleep promotion, support groups, etc. (c) manipulative and body-based practices: acupressure, acupuncture, chiropractic, massage, osteopathic manipulation, (d) biologically based practices (dietary supplements, herbal products,(e) energy medicines consists of electromagnetic fields, therapeutic touch, Qi gong, Reiki, and alternating fields [32].

CAM mind-body therapy, Yoga, contains a wide number of strategies that graduly harmonize body and mind, as collected by Patanjali in his Yoga Sutras [33]. Yoga has become an important part of Ayurveda, an ancient and oldest healing philosophy studied in India and represented in the Samhita and Susruta Samhita

Charaks [33, 34]. For thousands of years Yoga has been used by the Hindus and Buddhists to preserve both good health and spiritual practice (union of the soul with the divine self, salvation). Yoga 's integration with traditional cancer care is a patient-centered approach which fosters cancer patients ' physical, emotional and spiritual well-being. Despite several studies and evaluations that promote the effectiveness of yoga in lung cancer treatment, understanding and inclusion of yoga in conventional healthcare remain limited [35].

2.1.13. Prevention from lung cancer

2.1.13.1. Stop smoking

80% of active smokers are suffering from lung cancer in the USA. Half of them die due to lung cancer and other respiratory diseases caused due to smoking. Tobacco causes over five million deaths worldwide.The study conducted by Jerome Cornfield and his colleagues shows the direct relationship between the tobacco smokers and lung cancer. The study suggested that the single and best way to prevent lung cancer is to stop smoking [36].

2.1.13.2. Maintaining a healthy weight

Obesity (BMI≥30) is a major cause of cancer in many patients. Reducing your body weight and maintaining a healthy BMI can prevent you from developing cancer. The cohort study conducted by Calle EE shows that the death rates of participants having a BMI of at least 40 were 52% and 62% higher in men and women respectively in comparison to participants with normal weight [37]. Another study by Sung.H. showed that intentional weight loss resulted in a reduction from 24% to 76% in incidences of cancer [38].

2.1.13.3. Physical exercise

Physical exercise helps you to maintain your body weight, increase the oxygen consumption that eventually allows the body to work effectively. It also reduces the chances of developing cancer. A study by Hunk Dart shows that 30 minutes of moderate activity for five days per week or 20 minutes of vigorous activity for three days per week can show promising results in concern to prevention from cancer [39, 40].

2.1.13.4. Avoid radon exposure

The amount of radon in your surrounding highly depends on the rock and soil in your area. Peoples working in mines are most likely to get exposed to a high amount of radon released by the rocks**.** There are more chances of a person to develop cancer because of radon, if he/ she is a smoker. The combination of smoking and radon is proved more susceptible to develop cancer [41].

2.2. Advanced treatment Method of lung cancer

2.2.1. Flu-vaccine shots

Jenna H. Newman with his colleagues [42] conducted research that proved that inactivated influenza flu vaccine shots are beneficial in the treatment of patients having tumors in the lungs with a lung infection. The technique of flu-vaccine shots works on the principle of immunotherapy. According to the research, the body of a cancer patient develops two types of tumor cells, i.e., hot tumor and cold tumor. Immunotherapy works effectively on hot tumors, as they contain more immune cells than cold tumors. Research showed beneficial results to the patients when they are administered with intratumoral injections of the influenza flu vaccine. Administration of the flu vaccine starts converting cold tumors in the body into hot tumors. These hot tumors now can be treated with immunotherapy [42].

2.2.2. Dendrimer

A dendrimer is a nano molecule, which can perform more than one task at a time. A single dendrimer consists of a molecule that recognizes cancer cells, a therapeutic agent that kills cancer cells, a molecule that recognizes the signal of cell death. There are various factors in which dendrimers are proven better than conventional anti-cancer agents such as they carry more drugs to the site, as they are very small in size ranging from 1-100 nm that is favorable for pharmacokinetics and have better targeting potential. The most widely used types of dendrimers are polyamidoamine (PAMAM) and Polypropylene imine (PPI). The mechanism of the dendrimer is complex. In local treatments, amphiphilic dendrimers are used as they have a hydrophobic core and hydrophilic branches and the anti-cancer drug is encapsulated in the core. This solution is used in intratumoral injections. This makeup of dendrimer helps hydrophobic drugs to solubilize while leaving the drug unaltered. The anticancer drug is attached to the surface of the dendrimer by a covalent bond which helps the drug to dissolve properly and it also allows different hydrophobic anticancer drugs to attach while maintaining the controlled release [43, 44].

2.2.3. Nanoshells

Nanoshells can be of various shapes such as nanocluster, nanostar, nanocubes, branched. They have a dielectric core and are gold shell nanoparticles. These are being used in the diagnosis and treatment of photothermal cancer. The optical resonance of nanoshells can be tuned to the desired wavelength by manipulating its shape. Blood and tissues show maximum transmission at wavelengths just beyond the visible spectrum. After tuning the resonance to this region nanoshells can act as contrast agents and help in diagnosing tumors. When they are provided with the light, they become nano heat sources, which cause cell death and tumor remission. Nanoshells are designed to absorb radiation at various frequencies. They absorb certain types of radiation. Once the nanoshells are attached to the cancerous cells, only laser light is needed to treat cancer. Near-infrared (NIR) light passes through the body and reaches the nanoshell. The tuned nanoshell receives the NIR light and converts the light energy into heat, killing the cancer cells. There are various advantages of using nanoshells in cancer treatment as they are not toxic to healthy cells, they protect the drug-target interaction and they also enhance the drug absorption into cancerous and tumor cells [45-47].

2.2.4. Novel T-cell therapy

The immune system is the defense mechanism of our body. It protects us from harmful pathogens entering our body. Immunotherapy is also used in cancer treatment. But, it can only target specific types of cancer cells. Recently doctors were using CAR-T for treating cancer. In this process, the immune cells of the patient are taken and are genetically modified and injected back into the patient. The genetically modified T-cells will now hunt and kill the tumor cells. The drawback of this method is that it targets some types of cancer cells, it is not effective on solid tumors. The new novel T-cell treatment can recognize and differentiate between healthy and tumor cells. This new novel T-cell contains a unique receptor that makes it latch to cancer cells ignoring the healthy cells. This method is based on the surface molecule MR1, where the new T-cell is attached to. The surface molecule MR1 is present in all the cells in the body. But, they are present differently on the tumor cells which make the novel T-cell to effectively target those cells. The surface molecule MR1 acts as an indicator of distorted metabolism ongoing inside a tumor cell [48].

2.2.5. NaCl nanoparticles

Researchers observed that SCNPs (NaCl nanoparticles) can be used as a medium to deliver ions into the tumor cells to interrupt their internal environment, leading to cell lysis. This technique is well suited to deal with the localized destruction of cancer cells. The cell membrane restricts the cell to have low sodium concentration inside the cell and high sodium concentration outside the cell. Nanoparticles become the medium to insert SCNPs into the cells. The plasma membrane restricts the entry of sodium inside the cell, but SCNPs can enter the cell because they were not recognized as sodium ions by the plasma membrane. Once the SCNPs enter the tumor cell, they dissolve into a large number of sodium and chloride ions, and due to the gradient and the overwhelm protective mechanism the SCNPs are trapped inside the tumor cell which results in n the plasma membrane degradation and lysis of the cell. Due to the ruptured plasma membrane, the cell organelles leaks out, which signals the immune cells to come and fight with the pathogens. This technique is safe to normal cells because the tumor cells have higher sodium concentrations than normal cells to start with [49]

2.2.6. Nanobots

Nanobots are nanomachines or robots that can help in destroying the tumor cell. These nanobots are built according to the requirements. These nanobots contain molecules that can identify the tumor cells, which make nanobots cell-specific. Due to its specific nature, it does not harm other healthy cells near the tumor cells. The nanobots are made up of rectangular and flat DNA sheets. Thrombin, a blood-clotting enzyme and DNA aptamer that targets a protein found in high amounts on the surface of the tumor cells are attached to the surface and the sheet is folded up to form a hollow tube. After making the nanobot, it is injected into the artery. With the help of a DNA aptamer, the nanobot reaches the tumor cells, where the blood-clotting enzyme is released, stopping the blood flow to the tumor cells. These nanobots are used over other various modes of treatment because of several factors such as, they can undergo self-replication, they can remain functional for years, and most importantly they can eliminate or destroy cancer cells faster [50, 44].

3. CONCLUSION

In this review it was observed that there are so many advanced treatments which may be effective for lung cancer treatment. Integrated approach for lung cancer

treatment is advancing in today's world. Many therapies are available in the combination to provide more benefits to the patients. Lung cancer can be prevented and controlled but further clinical research is required to confirm the effectiveness of advanced therapies.

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