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Review Article

Comprehensive treatment of lung malignancy for meaningful survival

Laksmi Wulandari

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Authors' affiliations:
Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Jl. Mayjen. Prof. Dr. Moestopo no.6-8, Surabaya, 60286, Indonesia

Corresponding author:
Laksmi Wulandari
Email: laksmigts@yahoo.co.id

Abstract

The American Cancer Society estimates, in 2023 there will be an estimated 238,340 new cases of lung cancer in which 117,550 cases in men and 120,790 cases in women. Non-Small-Cell Lung Cancer (NSCLC) is a prevalent type of lung cancer, accounting for approximately 80% of all reported lung malignancy cases and characterized by a poor 5-year survival rate. Lung cancer detected in early stages with prompt diagnosis and appropriate treatment will improve the patient's life expectancy. According to current data, patients admitted to the hospital with lung cancer in an advanced stage. Platinum-based chemotherapy is widely regarded as the gold standard of therapy for patients with advanced lung cancer across the world. Chemotherapy not only eliminates cancer cells, but also affects actively proliferating normal cells, such as hematopoietic cells in the bone marrow. Stem cells that secrete granulocytes, erythrocytes and platelets in the peripheral circulation will be harmed as well. Further research and new discoveries are required for treatment approaches that are projected to reduce the problem of adverse survivorship bias and improve the quality of life for lung cancer patients. Several targeted therapies, such as EGFR tyrosine kinase inhibitors and ALK inhibitors, have demonstrated significant clinical success in treating NSCLC patients with the corresponding gene mutations.

Keywords: *ALK inhibitors, EGFR tyrosine kinase inhibitors, NSCLC, targeted therapy*

Abstrak

Menurut *The American Cancer Society*, perkiraan kasus baru kanker paru pada tahun 2023 adalah sekitar 238.340 kasus, dengan 117.550 kasus pada pria dan 120.790 kasus pada wanita. *Non-Small-Cell Lung Cancer* (NSCLC) merupakan jenis kanker paru yang sering terjadi (sekitar 80%) dari keseluruhan kasus keganasan paru-paru dengan tingkat kelangsungan hidup 5-tahun yang buruk. Jika kanker paru ditemukan pada stadium awal dengan diagnosis yang cepat dan pengobatan yang tepat, harapan hidup pasien akan lebih tinggi. Data saat ini menunjukkan bahwa pasien kanker paru datang sudah dalam keadaan stadium lanjut. Kemoterapi berbasis platinum dianggap sebagai pengobatan standar dunia untuk pasien dengan kanker paru stadium lanjut. Kemoterapi tidak hanya membunuh sel kanker tetapi juga memengaruhi sel normal yang secara aktif membelah diri seperti sel hematopoietik dalam sumsum tulang. Sel induk yang memunculkan granulosit, eritrosit, dan keping darah di peredaran darah tepi juga akan rusak. dibutuhkan lebih banyak penelitian dan terobosan baru untuk rencana pengobatan yang diharapkan dapat meminimalkan masalah *survivor-ship bias* yang merugikan dan mencapai peningkatan kualitas hidup bagi pasien kanker paru. Beberapa terapi yang ditargetkan, termasuk EGFR tirosin kinase inhibitor dan ALK inhibitor, telah menunjukkan keberhasilan klinis yang signifikan dalam mengobati pasien NSCLC yang memiliki mutasi gen yang sesuai.

Kata kunci: *ALK inhibitor, EGFR tirosine kinase inhibitor, NSCLC, terapi target*

Background

Lung cancer is included as one of the leading causes of cancer-related mortality annually. According to data provided by The Global Cancer Observatory (Figure 1), lung cancer (11.4%) ranks second in the incidence of new cases, following breast cancer (11.7%), and is the leading cause of cancer-related mortality (18%) worldwide. In Asia (Figure 2), lung cancer ranks first both in the incidence of new cases (59.6%) and in the mortality rate (61.9%).[1]

The American Cancer Society estimates, in 2023 there will be an estimated 238,340 new cases of lung cancer in which 117,550 cases in men and 120,790 cases in women. While the estimated number of cancer-related fatalities is roughly 127,070, with 67,160 deaths in men and 59,910 deaths in women.[2]

Lung cancer is not a sudden occurrence; rather, it is the result of a protracted process. Symptoms of lung cancer may lack visibility during the initial stages. The enhancement of community awareness on risk factors, symptoms, and treatment options is crucial. If lung cancer detected in early stages with prompt diagnosis and appropriate treatment, the patient's life expectancy will improve.

The Prevention of Lung Cancer

Prevention offers the greatest opportunity for combating lung cancer. Nevertheless, it is important to note that not every case of lung cancer may be avoided. There are controllable risk factors (such as pollution, lifestyle, smoking) and uncontrollable risk factors (such as age, gender, family history of cancer).[3]

The most effective strategy to lower the risk of developing lung cancer is by quitting smoking and avoiding exposure to secondhand smoke. At this point, smoking is the primary risk factor of lung cancer. It is widely recognized that approximately 80% of fatalities resulting from lung cancer may be attributed to smoking. Individuals who smoke are significantly more susceptible to developing lung cancer than nonsmokers. The risk increases with the duration and number of packs of cigarettes per day spent. Nonsmokers, but are inhaling secondhand smoke in the surrounding environment, have a higher chance of acquiring lung cancer. Secondhand smoke is the third leading cause of lung cancer in the United States.[4-6]

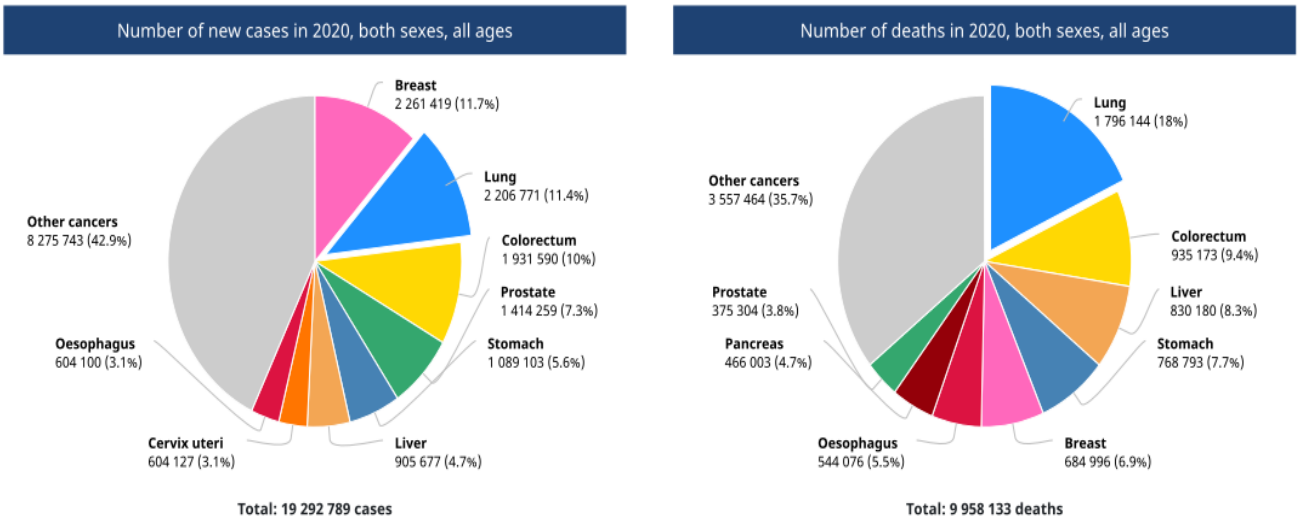
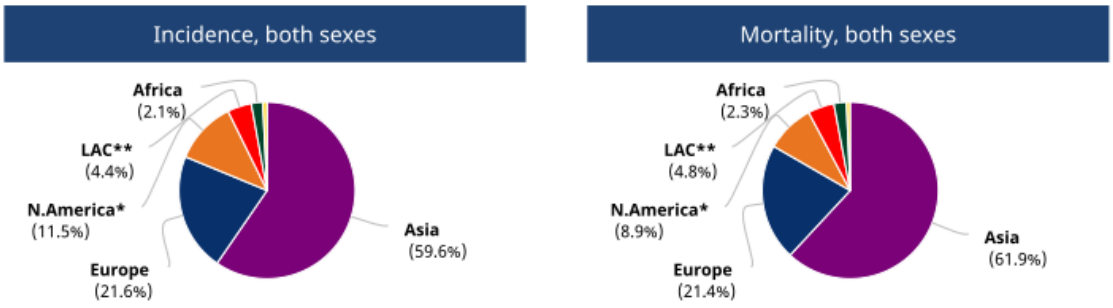


Figure 1. The number of new cases and mortality associated to lung cancer in 2020.[1]



Population	Number
Asia	1 315 136
Europe	477 534
*Northern America	253 537
**Latin America and the Caribbean	97 601
Africa	45 988
Oceania	16 975
Total	2 206 771

Population	Number
Asia	1 112 517
Europe	384 176
*Northern America	159 641
**Latin America and the Caribbean	86 627
Africa	41 171
Oceania	12 012
Total	1 796 144

Figure 2. The number of new cases and mortality associated to lung cancer in Asia.[1]

Early Detection of Lung Cancer

Lung cancer screening is recommended for individuals who are at a high risk but do not exhibit any signs or symptoms. In cases where an individual is diagnosed with lung cancer but remains asymptomatic, earlier detection of the disease may be possible. When lung cancer is detected in its early stages, still in limited size and not having metastasis, the probability of successful treatment is high. However, typically, lung cancer symptoms do not manifest until the disease has progressed to an advanced stage. Even when symptoms arise, many people mistakenly attribute them to other conditions, causing diagnosis to be delayed.[7]

The use of a low-dose computed tomography (LDCT) scan helps to detect abnormal areas in the lungs that may be cancerous. In contrast to chest X-rays, annual LDCT scans prior to the onset of symptoms has been shown to reduce the mortality rate associated with lung cancer.[8-10]

Hospital Admission of Patients in Advanced Stage

According to global statistics from 1990–2010, it was revealed that 43% of lung cancer patients were diagnosed with stage IV tumors, with a low 5-year survival rates of 10% for stage IVA and 0% for stage IVB (Figure 3).[11] In Surabaya, nearly 80% of lung cancer patients were diagnosed with stage IV tumors according to the data obtained from RSUD Dr. Soetomo in 2016-2018 (Figure 4).[12]

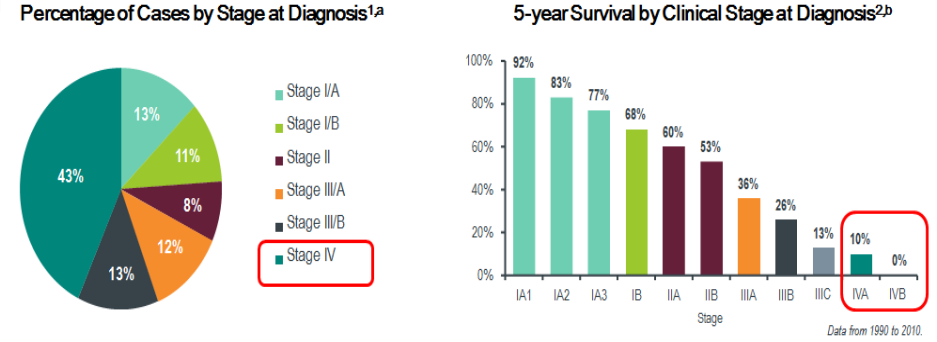


Figure 3. Global lung cancer staging at diagnosis and 5-year survival by stage.[11]

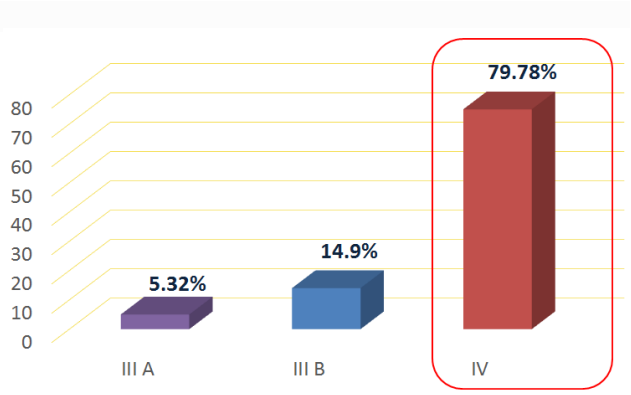


Figure 4. Lung cancer staging at diagnosis in RSUD Dr. Soetomo Surabaya between 2016-2018.[12]

Chemotherapy of Lung Cancer

Platinum-based chemotherapy is widely regarded as the gold standard of therapy for patients with advanced lung cancer across the world. A meta-analysis study by the Non-Small Cell Lung Cancer Collaborative Group in 1995 reported, that chemotherapy using platinum agents resulted in a significant enhancement in patient survival rates as compared to merely optimal supportive care (one-year survival rate of 15% vs 5%).[13]

Despite improvements in survival rates, nearly all patients experience relapse and even leading to death due to recurrent or relapsed NSCLC. Long-term survivors endure significant pulmonary, cardiovascular, and nervous system side effects while receiving treatment.[14]

Chemotherapy not only eliminates cancer cells, but also affects actively proliferating normal cells, such as hematopoietic cells in the bone marrow. Stem cells that secrete granulocytes, erythrocytes and platelets in the peripheral circulation will be harmed as well.[15,16] Therefore, further research and new discoveries are required for treatment approaches that are projected to reduce the problem of adverse survivorship bias and improve the quality of life for lung cancer patients.

Targeted Therapy of Lung Cancer

Non-Small-Cell Lung Cancer (NSCLC) is a prevalent type of lung cancer, accounting for approximately 80% of all reported lung malignancy cases and characterized by a poor 5-year survival rate. Numerous genetic and epigenetic abnormalities have been discovered in the development of NSCLC types.[17] Oncogenic driver mutations are primarily responsible for the activation of chemical signaling pathways that result in uncontrolled cell growth and proliferation which attributed to these abnormalities. Several mutation drivers, such as genes encoding for the epidermal growth factor receptor (EGFR), K-ras (KRAS), anaplastic lymphoma kinase (ALK), and others, have been identified in cases of NSCLC. A variety of targeted therapies, including EGFR tyrosine kinase inhibitors and ALK inhibitors, have demonstrated significant clinical success in treating NSCLC patients with the corresponding gene mutations.[18,19]

1. EGFR mutation-targeted therapy

   Epidermal growth factor receptor (EGFR) is a cell surface protein that promotes cell growth and division. Sometimes, individuals with NSCLC have an excessive number of EGFR, which accelerates cell growth. Drug agents that inhibit EGFR signals to cue cells to grow are known as EGFR inhibitors. Some of EGFR inhibitors are employed in the treatment of NSCLC, including erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib.[20-22]

   EGFR inhibitors have frequently demonstrated to reduce tumor size that can persist for several months or beyond. Eventually, however, the efficacy of these pharmaceutical agents diminishes for the majority of patients because cancer cells develop another mutation in the EGFR gene known as the T790M mutation.[20-22]

2. ALK rearrangement-targeted therapy
   Approximately 5% of individuals with NSCLC have ALK gene rearrangements. These alterations are frequently observed in nonsmokers or younger light smokers with adenocarcinoma subtype. ALK gene rearrangements produce abnormal ALK proteins which in turn promote the proliferation and metastasis of cancer cells. ALK-targeted therapy includes crizotinib, seritinib, alectinib, brigatinib, and lorlatinib.[20,21]

   The administration of these drugs to NSCLC patients with ALK gene alterations is frequently reduce the size of the tumors. Although this drug may help when chemotherapy has been ineffective, it may also be used directly as a substitute for chemotherapy in people with confirmed ALK gene rearrangements.[20,21]

Immunotherapy of Lung Cancer

Immunotherapy refers to the administration of pharmaceutical agents with the aim of enhancing the body immune system to recognize and eliminate malignant cells effectively. The crucial feature of immune system is the capacity to combat abnormal cells in the body. Immune cells, for this purpose, use checkpoint proteins that act as switches, that must be activated or deactivated to initiate the attack mechanism of the immune response. Cancer cells occasionally use these checkpoint proteins to evade the attack of host's immune system. The class of pharmaceuticals that specifically target checkpoint proteins are referred to as Immune Checkpoint Inhibitors.[23]

1. PD-1/PD-L Inhibitor
   Nivolumab, pembrolizumab, and cemiplimab are drugs that target PD-1, a protein on immune cells (T cells) that prevent these cells from attacking other cells in the body. Atezolizumab and durvalumab are pharmaceutical agents that specifically bind to PD-L1, a protein associated with PD-1, which is expressed on some tumor cells and immune cells. By inhibiting PD-1/PD-L1, these pharmaceutical agents have the capacity to augment the immune response against cancer cells, resulting in the reduction in size or deceleration of tumor progression. In some cases, before either of these drugs can be administered, a laboratory test is required to confirm the presence of PD-L1 expression, indicating that the drug will be more effective.[20,21]

2. CTLA-4 Inhibitor
   Ipilimumab and tremelimumab are likewise immune-stimulating medications, however they act by blocking CTL-4, another protein on T cells that helps to maintain the cells under control. These medications are not typically used as monotherapy, but rather in combination with PD-1 inhibitors (ipililumab with nivolumab, tremelimumab with durvalumab).[20,21]

Conclusion

The treatment of lung cancer, particularly the NSCLC type, is a challenge that is rapidly developing in the field of modern medicine. In the past, this condition was considered as a homogeneous disease, and all patients were treated in the same way. All stage IV NSCLC patients were treated exclusively with chemotherapy without patient selection based on histology or other biomarkers.

The application of platinum-based doublet chemotherapy was shown to increase overall survival for several months, while the level of toxicity continued to rise.[24] The implementation of personalized medicine for lung cancer therapy is driven by this factor. Collins described personalized medicine as an approach to guide clinical decisions associated to disease prevention, diagnosis, and treatments according to individual's genetic profile.[25] The patient's genetic profile can assist clinicians decide on the best course of treatment, including as the right dose or regimen.

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