

Advances in Lung Cancer Treatment

The number of potentially curative treatments for advanced, metastatic lung cancer has increased dramatically following the Cancer Moonshot investments that started in 2016. Many of these treatments target the effects of cancer-causing genetic variants, known as driver mutations. Immunotherapy treatments that release the full power of the patient's own immune system produce amazing results. Advances in radiation therapy yield markedly better results with fewer treatments, reducing the need for surgical intervention. Emphasis on cancer prevention, earlier identification through cancer screenings, and highly effective treatments that can precisely target the characteristics of a patient's specific tumor have had a significant impact on outcomes. The field of oncology is changing dramatically, and agencies that recognize this phenomenon and respond will have the competitive edge. We are no longer just getting patients ready to accept hospice; we need to also focus on getting patients ready for longterm survival with the highest possible quality of life. Understanding the basics about cancer treatment options today is a core competency for home health clinicians and managers. There is an emerging need for home health nurses, therapists, and social workers with advanced education and certification in oncology who can anticipate, identify, and clearly communicate potential disease and treatment-related concerns to other members of the healthcare team. Teaching patients how to maintain functional status, manage symptoms, and to prevent avoidable complications promotes a high quality of life as well as long-term survival.

cancerous tumor begins when there is a loss of controlled reproduction; a single cell mutates and clones itself. Mutations happen all the time, but in most cases, the damaged cell is repaired, unable to reproduce, or is destroyed by the immune response. Cancerous cells that produce tumors and blood cancers are those that successfully escape the immune mechanisms that identify and destroy damaged cells. When cancer cells escape detection, it is referred to as immune evasion (Anichini et al., 2020).

Effective, personalized treatment of a cancer requires very specific information about the characteristics of each tumor. The primary site is determined by examining the type of cells found on biopsy to identify the vital organ or tissue from which the cancerous cells originated. For example, a tumor in the lung may prove to be primary lung cancer, or a metastasis from another primary site such as the kidney or breast. If the cancer originated in the lung or bronchial tissue, it is classified as a primary lung cancer. If the cell type is from the kidney, it would be described as a kidney/renal cancer with metastasis to the lungs.

In the United States, death rates for all cancers dropped by approximately 31% between 1991 and 2018. The factors that appear to have had the greatest impact are reductions in cigarette smoking, detection at earlier stages due to improved screening tools, and more effective treatment options (American Cancer Society [ACS], 2022).

Lung cancer provides an excellent example of a type of cancer where treat-

ment developments have resulted in extended survival. The three most common categories for lung cancer are non small cell lung cancer (NSCLC), small cell lung cancer, and carcinoid. Lung tumors are also categorized by the histological subtype (Figure 1). Adenocarcinomas, whether found in the lung, colon, breast or elsewhere, arise from a cell that produces mucous, for example, the alveoli in the lungs or mucous producing cells in the colon. Squamous cell carcinomas arise from epithelial cells in tissues and organs, for example,

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cells in the top layer that lines the bronchus and airways or in the outer layer of skin cells (Brown et al., 2018). Carcinoid (neuroendocrine) NSCLC lung tumors produce hormones or substances similar to hormones. For example, a lung tumor may produce too much cortisol and cause Cushing's syndrome, or produce serotonin resulting in diarrhea, flushing, and wheezing. Tumors that produce histamine may cause prolonged flushing of the skin, intense itching, and anxiety for several hours to days (Pandit et al., 2021).

In the past, most patients with advanced, life-limiting metastatic cancer were referred to hospice programs or home health until the patient and family were "ready for hospice." Today, many of the cancer-causing genetic variants can be targeted with therapies that result in longterm, progression-free survival/remission. Immunotherapy treatments release the full power of the patient's

own immune system to identify, attack, and destroy tumor cells. These treatments are producing amazing results.

Clinician understanding of current treatment options is crucial to helping patients develop realistic goals and continue interventions that will help achieve those goals. Home care agencies that address the full range of oncology support will have the competitive edge. Thus, there is a need for home health nurses, therapists, and social workers to obtain advanced education and certification in oncology. This article discusses recent advances in lung cancer treatment that have achieved long-term remission and survival.

An Explosion of Advances

Management of cancer has undergone a transformation, with an explosion of advances since passage of the United States 21st Century Cures



Act in 2016. The "Cancer Moonshot" invested \$1.8 billion over 7 years with dramatic results (National Cancer Institute, 2021). Major advances in immunohistochemistry and whole genome sequencing provide crucial information about tumor cells, allowing for personalized treatment protocols (Malapelle et al., 2020). Data on prevalence, results of clinical trials, and patient-specific responses to treatments have been compiled into large knowledge bases. Some companies that provide genetic and immunohistopathology testing even use artificial intelligence to identify probable outcomes for various targeted therapies based on the patient's tumor characteristics (Petak et al., 2021). National and international evidence-based treatment guidelines are updated regularly and provide options to assist oncologists and patients to determine the best possible individualized treatment plan.

There are also significant advances in radiation treatments. Stereotactic ablative radiation therapies use highly focused intense beams to target tumor with minimal adjacent tissue damage, reducing the need for surgery. The rapid reduction in tumor size after three focused radiation fractions (versus 10 with older methods) can dramatically improve quality of life when used to reduce pain due to nerve compression (Zeng et al., 2019).

An excellent example of a type of cancer where recent developments in treatment options have resulted in extended survival is NSCLC. Unfortunately, despite rapid advances and recently introduced treatment options, 5-year relative survival at diagnosis for lung cancer remains low at 22%; however, this is a marked improvement over the rate of 15% for those diagnosed in the 1990s (ACS, 2021).

Preventive screening for lung cancer is a recent development. Historically, late diagnosis contributed to poor outcomes. At the time of diagnosis, 43% of patients present with stage IV, distant metastasis, and 17% were at stage 3, localized metastasis (Figure 2). Signs and symptoms of lung cancer such as cough, hoarseness, fatigue, and shortness of breath are nonspecific and may be attributed to other factors. Pain related to metastasis may be the first symptom that causes the patient to seek help. Metastasis within the lungs and to lymph nodes, bone, liver, adrenal glands, nervous system, and/or brain is common (Zhu et al., 2020).

As of 2021, screening with low-dose computerized tomography is recommended for individuals at high risk (age 50 or over with a 20 pack/year or greater smoking history). Exposures to radon and occupational hazards, patient and family history of cancer, and preexisting chronic lung disease should also be part of the risk assessment. Unfortunately, the lack of widespread screening tests reduces the possibility of identifying most lung cancers at the earliest, and most treatable stages.

Treatment Decisions

Treatment decisions in oncology may include surgery, interventional radiology, radiation, rehabilitation services, nutritional interventions, pharmacological options, emotional and spiritual support, energy-based therapies, as well as complementary and alternative methods. Most importantly, treatment decisions are made based on what the patient does and does not want. Medications may be used alone or in combination with other agents, depending upon recommended guidelines and based on consideration of:

- The type of primary cancer/extent of metastasis,
- Results of diagnostic tests,
- Biological, genetic, and histocompatibility characteristics of the cellular mutations,
- Overall condition of the patient/comorbidities/ contraindications,
- Symptoms that need to be managed,
- Availability of clinical trials,
- Financial considerations/insurance status. (Brown et al., 2018; Hanna et al., 2021; National Comprehensive Cancer Network [NCCN] 2021a).

Figure 1. Types of lung cancer

Categorization of Primary Lung Cancers:

- Non small cell lung cancer (NSCLC) approx. 80%-85%
- Small cell lung cancer (SCLC) approx. 10%-15%
- Carcinoid (neuroendocrine) tumors approx. 5%

Metastatic tumors from other primary locations are not considered "lung cancers."



Histological Subtype NSCLC:

- Adenocarcinoma—arises from mucous producing cells (alveoli)
- Squamous cell carcinoma—arises from the epithelial cells that line the airways (bronchus)
- Large cell (undifferentiated) carcinoma

Immunohistochemistry (IHC) assay and whole genetic sequencing are obtained to identify and personalize treatment options.

Artist Kateryna Kon Stock Illustration - Lung cancer, 3rd illustration and photo under miscroscope, light micrograph showing lung adenocarcinoma. Clip Art gg119533725. Licensed through https://gograph.com

Brown, N. A., Aisner, D. L., & Oxnard, G.R. (2018). Precision medicine in non-small cell lung cancer: current standards in pathology and biomarker interpretation. American Society of Clinical Oncology. https://ascopubs.org/doi/pdf/10.1200/EDBK_209089

Malapelle, U., et al. (2020). From traditional histology to next-generation pathology: a review of the workflow for the characterisation and molecular profiling of non-small cell lung cancer samples. *European Medical Journal, February 24, 2020*. DOI/10.33590/emjoncol/19-00107. https://emj.emg-health.com/wp-content/uploads/sites/2/2020/02/From-Traditional-Histology-to-Next-Generation-Pathology.pdf





* All racial groups include Hispanic

National Cancer Institute. (n.d.). Surveillance, epidemiology, and end results program. Cancer stat facts: lung and bronchus. https://seer. cancer.gov/statfacts/html/lungb.html

Chemotherapy

Chemotherapy agents are cytotoxic chemical agents that are synthesized or extracted from a variety of sources. The goal is to kill cancer cells, but other cells may also be affected resulting in hair loss, neutropenia, anemia, and oral lesions. Chemotherapy agents such as Docetaxel (Taxotere®) or Gemcitabine (Gemzar®) may be used for NSCLC (NCCN, 2021b). Until recently, cytotoxic chemotherapy agents were first-line treatment. Dramatic improvements in technology are happening, and as tumor-specific information becomes widely available, it is likely that the use of chemotherapy will decrease.

Targeted Therapies

Abnormal proteins produced by the mutated genes "feed" the tumor and help it grow. Some treatments bind with and inactivate the abnormal proteins so they can't feed the tumor cells. Other treatments attach to and block the receptors that the abnormal protein binds to on the outer membrane of the cell. Other treatments enter the abnormal cells and interfere with the metabolic processes that promote cell reproduction. If the targeted therapy works, cancer growth can be halted or slowed.

Targeted therapies fall into one of two broad categories. If the generic name of the medication ends in "ib," as with Osimertinib (Tagrisso[®]), the

drug is a small molecule inhibitor, designed to enter the cancer cell and block the "targeted" metabolic process that promotes abnormal cell reproduction. If the name ends in "mab," the drug is a monoclonal antibody that will bind to specific "target" antigens located on the outer membrane of the cancer cell. Because they are designed to attack a specific target, these medications tend to be more effective than cytotoxic chemotherapy agents that indiscriminately affect most fast-growing cells.

Pathological Gene Variants

There are 10 common pathological gene variants known to cause NSCLC (as well as several other types of cancer), with eight that have treatments that "target" the cancer cells (Figure 3). The most common oncogene, KRAS (pronounced kay ras) is found in 25% of all cancers and 32% of lung cancers. There is only one currently approved biological that specifically targets the KRAS G12C mutation, Sotorasib (Lumakras[®]), approved in 2021. Sotorasib binds with the mutated KRAS and selectively destroys the cancer cells. Serious treatment-related adverse effects include hepatotoxicity, pneumonitis, interstitial lung disease, gastrointestinal disorders, and musculoskeletal pain. The cost is approximately \$18,700 per month (Drugs.com, 2021).



Figure 3. Pathological gene variants: Prevalence and targeted therapies (TT) for non small cell lung cancer (NSCLC)

American Cancer Society. (2021, September 16). Targeted drug therapy for non-small cell lung cancer. https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html

American Lung Association. (2021, October 14). Lung cancer biomarker testing. https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/symptoms-diagnosis/biomarker-testing

National Comprehensive Cancer Network. (2021, October 29). NCCN guidelines version 7, 2021. Non-small cell lung cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Pathological variants of the epidermal growth factor receptor oncogene are found in about 15% of NSCLCs. In many cases, tumor cells mutate further and become resistant to the older, first-generation therapies. For this reason, NCCN recommends using a third-generation biological, Osimertinib (Tagrisso[®]). This treatment blocks production of an enzyme necessary for cell survival, and the cancer cells die (Astra Zeneca, 2020; NCCN, 2021b). Osimertinib is an oral small molecule inhibitor. Serious adverse events include pneumonitis, cardiomyopathy, erythema multiforme major, and visual changes due to keratitis, stomatitis, or infection. Typically, one tablet daily is continued for up to 3 years unless there is disease progression or intolerable adverse events (Astra Zeneca, 2020). The cost is around \$15,877 per month (Drugs.com, 2021).

The intravenous monoclonal antibody Amivantamab-vmjw (Rybrevant[®]) was approved in 2021 for use after metastatic disease progression with platinum chemotherapy treatment. This drug binds to receptors on the outside of the cell and disrupts the function of genes and targets the cancer cells for destruction by the patient's immune cells. Serious adverse effects include pneumonitis, interstitial lung disease, infusion reactions, skin reactions, vision changes, and embryo-fetal toxicity. The cost is approximately \$12,500 per treatment (Drugs.com, 2021).

Pathological variants of the anaplastic lymphoma receptor tyrosine kinase gene are found in approximately 6% of NSCLCs and there are several targeted therapies available, including Alectinib, Brigatinib, Crizotinib, and Lorlatinib. Serious adverse events for these drugs include pneumonitis, interstitial lung disease, hypertension, bradycardia, hyperglycemia, hepatotoxicity, renal impairment, visual disturbances, and embryo-fetal toxicity. Therapy is oral and continues indefinitely unless there is disease progression while receiving the medication or dose-limiting toxicity (Genentech, 2021). Costs for these five medications range from \$11,200 to \$19,500 per month (Drugs.com, 2021).

Vascular endothelial growth factor is a protein that is released in arterial disease when tissue cells are not getting enough oxygen. With cancer, tumor growth tends to stall when the size reaches 1 to 2 mm in diameter because the oxygen supply to the rapidly proliferating cells is inadequate. Vascular endothelial growth factor stimulates growth of new blood and lymph vessels to create an independent blood supply for the growing tumor. Blocking it reduces the risk of metastasis, and the size of existing tumors may also decrease (Genentech, n.d.). Treatment to block vascular endothelial growth factor is usually not used unless there is disease progression.

If there is disease progression with the current treatment, Ramucirumab, a monoclonal antibody administered every 2 weeks could be initiated. This targeted therapy is prescribed indefinitely unless there are toxic side effects or disease progression. Serious adverse effects include hemorrhage, gastrointestinal perforation, arterial thromboembolic events, posterior reversible encephalopathy syndrome, infusion reactions, and hypertension. The list price is \$13,400 to \$15,075 per month (Lilly, 2021).

Immune Checkpoint Inhibitors

The human immune system is very powerful, with checkpoints that maintain balance and prevent autoimmune disease. Most potentially cancerous cells are silently eliminated, and cells with pathological variants able to evade the immune response can stay dormant or reproduce to form cancers. Immune Checkpoint Inhibitors are firstline treatment for patients with NSCLC who do not have pathological variants. Checkpoint Inhibitors target one of two pathways, programmed death, or cytotoxic T lymphocyte-associated antigen-4. Immune-mediated adverse effects may occur, including myocarditis, pneumonitis, hepatotoxicity, nephritis, colitis, adrenal insufficiency, hypophysitis (pituitary), thyroiditis, toxic epidermal necrolysis, or Stevens-Johnson syndrome.

Some cancers produce proteins that prevent T cells from killing the damaged tumor cells by blocking the programmed death receptors on the surface of the T cell. Monoclonal antibodies such as nivolumab (Opdivo®) and pembrolizumab (Keytruda®) bind with PD-1 receptors on the T cells so that the T cells can see, attack, and

destroy the tumor. T cells that are converted to memory T cells after exposure to the cancer cells will continue to circulate and will recognize the cancer if it reoccurs (Bristol Myers Squibb, 2021a; Merck Sharp & Dohme, 2021).

CTLA-4 is a glycoprotein expressed by T cells when they become activated. CTLA-4 binds to receptors on the outside of the T cell and this controls both T cell activity and proliferation. Ipilimumab (Yervoy[®]) is a monoclonal CTLA-4 blocking antibody that binds to the receptors (Bristol Myers Squibb, 2021b). The result is a powerful attack on tumor cells. When the "checkpoints" that prevent the individual's T cells from attacking normal cells are removed, the patient's immune response kicks into high gear with a systemic inflammatory response.

Serious, and potentially life-threatening immunemediated adverse effects may occur with blocking immunotherapies. These include pneumonitis, colitis, nephritis, hepatitis, thyroiditis, and toxic skin reactions. It is important for the home health team to be alert to changes in condition, including cough, shortness of breath, abdominal pain, diarrhea, bloody stools, decreased urine output, blood in the urine, increased fatigue, tachycardia, hyper or hypotension, musculoskeletal pain, yellowing of the skin or sclera, rash or sloughing of skin. If labs are ordered, they need to be drawn and delivered early in the day and sent to the prescriber before the treatments are administered. The treatments may continue for up to 2 years unless there is disease progression or intolerable side effects (Bristol Myers Squibb, 2021a; Merck Sharp & Dohme, 2021).

Financial Toxicity

Surviving cancer, long- or short-term, is expensive. Patients with metastatic disease are often referred to home care, so it is important for clinicians to understand the impact. The high costs of targeted therapies and immune checkpoint inhibitors continue for years. Survivorship plans also require regular and timely follow-up for oncology visits, lab tests, scans, therapy visits and treatments. It is estimated that in the United States, 16% to 49% of people requiring cancer treatment experience financial difficulty related to treatment costs (Thomas et al., 2019). Although most pharmaceutical companies have financial assistance programs, there are often income guidelines, insurance requirements, governmental carve outs, and other



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restrictions. There are also charitable organizations, including foundations created by several pharmaceutical companies that may be able to help (McMullen, 2019).

The costs of care undoubtedly cause hardship and it is important for clinicians to assess for anxiety, depression, and even family conflict. Loss of income and health insurance may further compound the issues. Most pharmaceutical companies do provide some form of copayment relief, but it is difficult to understand the rules, complete the paperwork, gather the necessary financial data, coordinate with the oncologist, and obtain the necessary prescriber signatures. Home health and oncology center social workers can be invaluable in helping patients navigate the various funding sources. Communication between home health and oncology teams is essential to avoid duplication of effort.

Palliative Treatment Considerations at End of Life

Manufactures of the chemotherapy, targeted therapies, and immunotherapies recommend that treatments stop when disease progression is identified. Riaz et al. (2020) indicated that patients for whom the treatments are continued into the last 30 days of life have more emergency room visits, hospitalizations, critical care admissions, and in-hospital deaths. Continued use of these treatment increases adverse effects and costs, and when administered during the last 30 days, do not improve quality or length of life. Such patients are also less likely to receive hospice care (Riaz et al., 2020). Hospice care provides a comprehensive program that includes access to a team skilled in management of uncomfortable symptoms, psychosocial and spiritual support, and provision of equipment, supplies, and medications needed to ease suffering.

Summary

Cancer Moonshot funding, technological advances in genetics and immunohistochemistry, and an explosion of highly effective targeted therapies and immune checkpoint inhibitors have changed management of cancer. Oncologists are now able to develop personalized treatment plans that target specific characteristics of a given person's tumor with precision. The goal for patients receiving these treatments is progression-free survival with the highest possible quality of life. Whereas patients with advanced, extensively metastatic NSCLC cancer would have been referred to hospice in the past, extension of length and quality of life is now a realistic goal with the availability of targeted immunotherapies. Thus, there is an urgent need to increase the numbers of home health nurses and therapists who understand the complexities involved in caring for oncology patient. 🌰

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