PANHANDLE HEALTH

A QUARTERLY PUBLICATION OF THE POTTER-RANDALL COUNTY MEDICAL SOCIETY

SPRING 2022 | VOL 32 | NO. 2

What's New in Oncology

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President's Message:
New Year, Old Challenges

by Evelyn Sbar, MD, FAAFP, AQH

Welcome to a New Year and new issue of *Panhandle Health* Magazine! I don't know if we are yet entering a new norm, but I am happy to read about something other than COVID for a change.

Our new cadre of officers is excited about what the next few years may bring, but concerned as well. The Potter-Randall County Medical Society meetings have gotten slim through the pandemic, and Texas Medical Association (TMA) memberships are down. I will be the first to admit that politics and advocacy have left me frustrated (if not dumbfounded) as of late. However, today's "News of the Day" reminds me why my dollars and my time will continue to support TMA: "Court Considers Attack on Noneconomic Damages Cap [Tort Reform]."

Prior to 2003, Texas lived in a constant medical malpractice crisis. Ridiculously high premiums caused physicians to leave their practices and further exacerbated access to care issues. Thanks to a hard-earned battle by TMA and others, medical malpractice caps were created, malpractice premiums dropped, and the number of practicing Texas physicians increased significantly. Now, this 2003 tort reform legislation is in peril. A current lawsuit that could abolish all this hard work has gone to trial on February 9, 2022 and could land in the U.S. Supreme Court. There are also 13 other separate cases challenging the cap. Without it, liability premiums will once again skyrocket, we will lose practicing physicians and patients will be stranded without care. Loss of the cap also puts state autonomy laws on the chopping block and in the hands of the federal government.

For further information check out this site: (https://urldefense.com/v3/__https://www.texmed.org/TexasMedicineDetail.aspx?id=58464__;!!PZU9J6Y!NULLjDjSk-0WIQUKiALmCYIq_fnUAIKfo5G-YbDjfzRQ5JhQIiRdhZs51XyGRIX-jZ92j$)

Being a physician in this day and age has ever changing hurdles. Please help us avoid losing the progress we have made. Support your Medical Society! Our PRCMS meeting calendar can be accessed at: at https://urldefense.com/v3/__http://www.prcms.com__;!!PZU9J6Y!NULLjDjSk-0WIQUKiALmCYIq_fnUAIKfo5G-YbDjfzRQ5JhQIiRdhZs51XyGRIcuHI6pm$ or you can reach Cindy Barnard at 806-355-6854.

You can join TMA at https://urldefense.com/v3/__http://www.texmed.org__;!!PZU9J6Y!NULLjDjSk-0WIQUKiALmCYIq_fnUAIKfo5G-YbDjfzRQ5JhQIiRdhZs51XyGRIcicrbQ-$

Hope to see you around soon!

UPCOMING EVENTS 2022

TexMed 2022
Apr. 29-30, 2022
Hilton Americas-Houston
Houston, TX

Fall Conference
Sept. 16-17, 2022
Hyatt Lost Pines
Austin Area, TX

Advocacy Retreat
Dec. 2-3, 2022
Omni Barton Creek
Austin, TX

Executive Director's Message

by Cindy Barnard, Executive Director

Groundbreaking discoveries in oncology research and treatment are making a real difference for people around the world. The National Cancer Institute has at least 50 designated Comprehensive Cancer Centers with state-of-the-art science, clinical studies and treatment. Physicians and scientists now closely collaborate so that patients are able to have excellent care. At the same time, doctors and the scientific community are diligently working to find more effective methods to "prevent, control, and ultimately cure cancer." This issue of *Panhandle Health* addresses "What's New in Oncology" which hopefully is of interest to virtually all of our readers.

Due to the ever-present Coronavirus, and now the Omicron variant, we cancelled our 119th Annual Meeting of the Potter-Randall County Medical Society, traditionally held in January or February. The new President of PRCMS is Evelyn Sbar, MD, President-Elect is Nicole Lopez, MD, and Secretary-Treasurer is Tetyana Vasylyeva, MD.

On March 30th, we will celebrate Doctors Day, which was first observed in Winder, Georgia in 1930. According to Wikipedia, Eudora Brown Almond, a physician's wife, decided to declare a day in honor of all doctors. The red carnation was chosen as the symbolic flower for National Doctors Day. In 1958, a Resolution commemorating Doctors Day was adopted by the U.S. House of Representatives, and in 1990, legislation was introduced both in the House and Senate to establish National Doctors Day. In 1991, President George Bush signed S. J. RES #336, which became public law 101-473, forever designating March 30th as National Doctors Day. President Bush wrote in the Proclamation, "In addition to the doctors whose names we easily recognize, there are countless others who carry on the quiet work of healing each day in communities throughout the United States – indeed, throughout the world. Common to the experience of each of them, from the research specialist to the general practitioner, are hard work, stress, and sacrifice. All those who serve as licensed physicians have engaged in years of study and training, often at great financial cost. Most endure long and unpredictable hours, and many must cope with the conflicting demands of work and family life." President Bush urged that all Americans "observe this day with appropriate programs and activities."

We continue to monitor and follow the Covid guidelines recommended by the CDC and our state and local health departments. The well-being of our friends and families is our top priority. Despite the excellent efforts in vaccinating our residents, our Health Department continues to ask us to wear our masks and practice social distancing. These small steps are not that difficult, and you may be saving not only your own life, but that of your neighbors. PLEASE BE SAFE!

Finally, PRCMS appointments to our Boards and Committees are now ongoing. If you have an interest in serving on a committee, please call the Society office at (806)355-6854. The core of the Society is its volunteers – the physicians who volunteer for committees and board positions, working on behalf of their colleagues. We truly need YOU!

POTTER RANDALL COUNTY MEDICAL SOCIETY (PRCMS) OFFERS HELP TO TROUBLED PHYSICIANS

If you, or a physician you know, are struggling with addiction, depression or burnout and are unsure what to do or whom to contact, the Potter-Randall County Medical Society is here to help. We offer face-to-face confidential sessions with the PRCMS Physician Health and Wellness Committee, made up of your physician peers who know and understand recovery. Please don't struggle alone when help is a phone call or an email away. Whether you are calling for yourself, your practice partner, or as a family member of a physician, contact Cindy Barnard, PRCMS Executive Director, at 806-355-6854 or prcms@suddenlinkmail.com. Membership in PRCMS is not required.

Message from the Potter-Randall County Medical Alliance

by Tricia Schniederjan, President

This past December, the Alliance teamed up with the Northside Toy Drive organization. The Northside Toy Drive is an annual event that began in 2013 and has grown to provide Christmas toys for so many children in need in Amarillo. The Palo Duro High School gym was completely full of toys and children; their families began lining up early in the morning and waited for hours for their turn. There were many scooters, hoverboards, bikes, roller skates and skateboards to choose from, and the Alliance was there fitting and handing out helmets to go along with all of them. We loved being able to provide protection for these children. We gave away over 200 helmets and plan on joining them again next December to do the same. The event was a huge success!

If you'd like to join us, we could really use the volunteer help. An email will be sent to sign-up. Please look for that next November. In addition, if you would like more information on the Northside Toy Drive, you can visit their website: northsidetoydrive.org.

Our Next Issue Of
Panhandle Health
Features:
Social Determinants of Health

Advances in Immuno-Oncology

by Praveen Tumula, MD

Introduction

With recent success stories in melanoma, breast cancer, gastric cancer, renal cell carcinoma, prostate cancer, Hodgkin's lymphoma, squamous cell lung cancer, and other malignancies, immunotherapy has emerged as perhaps the most paradigm-changing treatment strategy to occur in oncology in the last 35 years. Modern immunotherapy started when Dr. Edward Jenner began using cowpox as a vaccine against smallpox, experimenting on nonexposed children, including his own. This great success back in 1796 was followed by the "father of cancer immunotherapy," surgeon William B. Coley, who achieved "durable disease control" in some cases with his "Coley's toxin," derived from bacteria.

Let's delve into some basics in the battle against cancer. Various immune cells – including lymphocytes (CD4 and CD8 lymphocytes), NK cells, Tregs, macrophages, and dendritic cells (which are antigen presenting cells considered as guardians of the immune system) – all participate in the battle against cancer, or "cancer immunoediting." Broadly speaking, cancer immunoediting has 3 phases – elimination, equilibrium and escape or evasion. In the elimination phase, host immunity works to destroy developing tumors long before they become clinically apparent. If this phase goes to completion, then the host remains free of cancer, and elimination thus represents the full extent of the process. If, however, a rare cancer cell variant is not destroyed in the elimination phase, it may then enter the equilibrium phase, in which its outgrowth is held in check by immunologic mechanisms. Editing of tumor immunogenicity occurs in the equilibrium phase. Equilibrium may also represent an end-stage of the process if cancer immunoediting restrains growth of occult cancers for the lifetime of the host. However, because of constant selection pressure placed on genetically unstable tumor cells held in equilibrium, tumor cell variants may emerge that (i) are no longer recognized by adaptive immunity, (ii) become insensitive to immune effector mechanisms with infiltration by Tregs, or (iii) induce an immunosuppressive state within the tumor microenvironment by manipulation of cytokines or upregulation of immune check point molecules. These tumor cells may then enter the escape phase to cause clinically-apparent cancer.

The various co-inhibitory signals or "immune checkpoint" molecules – including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death-1 protein (PD-1), TIM3, and LAG3 – have been recognized as key molecules contributing to escape from immune control and thus have become targets for cancer immunotherapy.

Checkpoint inhibitor immunotherapy

1) PD-1 and PD ligand 1/2: Programmed cell death 1 protein (PD-1) is a transmembrane protein expressed on T cells, B cells, and NK cells. It is an inhibitory molecule that binds to two programmed cell death ligands, PD-L1 and PD-L2. PD-L1 is expressed on the surface of multiple tissue types, including many tumor cells, as well as hematopoietic cells; PD-L2 is more restricted to hematopoietic cells. The PD-1 receptor-ligand interaction directly inhibits apoptosis of tumor cells, leads to peripheral T effector cell exhaustion, and promotes conversion of T effector cells to Treg cells. Therefore, activation of PD-1 receptor promotes cancer cell growth. On the other hand, blocking this interaction with a PD-1 inhibitor would lead to death of cancer cells, would rev up effector T-cells to attack cancer cells, and would suppress the deleterious Treg cells. The last 2 features would enhance immunoregulation of cancer cells by the patient's T cells. Based upon prolongation of overall survival in phase III trials and durable responses in phase I and II studies, antibodies inhibiting PD-1 (pembrolizumab, nivolumab, dostarlimab) and PD-L1 (atezolizumab, ave-

| *continued on page 10*

lumab, durvalumab) have been approved for a number of clinical indications and are being evaluated in multiple other malignancies.

PD-1 inhibitors have been approved in numerous cancers over the past couple of years including breast, cervical, colorectal, skin (squamous cell, merkel cell, melanoma), esophageal, gastric, head and neck, Hodgkin's, mesothelioma, lung cancer, mediastinal B cell lymphoma, kidney, uterine, bladder and microsatellite unstable/ tumor mutation burden high cancers.

2) CTLA-4: CTLA-4 can be broadly considered a physiologic "brake" on the CD4+ and CD8+ T cell activation that is triggered by APCs. The anti-CTLA-4 antibody ipilimumab was the first immune checkpoint inhibitor to be approved, based upon its ability to prolong survival in patients with metastatic melanoma. It is also now approved as adjuvant therapy for high-risk melanoma as an alternative to interferon.

New targets for cancer immunotherapy

Increased understanding of the underlying immunologic mechanisms has led to the identification of several additional potential targets for checkpoint inhibition.

1) LAG3 – Lymphocyte activation gene 3 (LAG3) is expressed by B cells, some T cells, NK cells, and tumor infiltrating lymphocytes (TIL). The LAG3 protein enhances Treg activity by binding major histocompatibility complex (MHC) class II and interfering with T cell differentiation and proliferation. Since Treg cells suppress immune-mediated killing of cancer cells, activation of LAG3 encourages cancer growth. Inhibiting LAG3, on the other hand, would help the host's immune system kill tumor cells. The combination of relatlimab, a LAG3-blocking antibody, with the PD-1 blocker nivolumab has been evaluated in advanced melanoma.

2) CD47- The antigen CD47 may be expressed on tumor cells, protecting them from phagocytosis by macrophages (i.e., the cancer tells the macrophages "Don't eat me!"), and is therefore a potential target for anticancer therapy. Hu5F9-G4 (a humanized anti-CD47 monoclonal antibody) or magrolimab, in combination with rituximab (an anti-CD20 monoclonal antibody), was associated with objective response in half (and complete response in more than one-third) of non-Hodgkin's lymphoma patients.

CART/Adoptive T cell therapy

1) Adoptive T cell therapy: These therapies involve manipulating T cells *ex vivo* to make them more reactive to specific antigens on tumor cells. These are currently studied in various solid cancers.

2) Chimeric antigen receptor (CAR) therapy: CAR-T cells are genetically modified T cells, where a patient's own (autologous) T cells are manipulated *ex vivo* to express the antigen-binding domain from a B cell receptor that is fused to the intracellular domain of a CD3 TCR (CD3-zeta). As a result, recognition of a specific cell surface antigen activates T cell response independently of MHC recognition. Clinical trials targeting CD19, the pan-B cell antigen, have shown remarkable success and have achieved FDA approval in B cell acute lymphoblastic leukemia (B-ALL), lymphomas (both Hodgkin's and non-Hodgkin's), and multiple myeloma.

T cell engagers

1) BiTE- Bispecific T cell engagers: Conceptually, bispecific T cell engager antibodies (BiTEs) function as linkers between T cells and specific target antigens. They consist of a protein fragment containing two separate single-chain variable regions. One end recognizes CD3, which is expressed on all T cells, and the other end recognizes the target antigen. BiTEs thus aim to induce cytotoxic T cell-mediated tumor eradication. Because BiTEs are not MHC-specific, they can be administered to all patients regardless of human leukocyte antigen (HLA) type and do not require patient-specific processing. In addition, since many different T cell subtypes express CD3, BiTEs induce a polyclonal response; cytotoxic T cells, Th1 and Th2 CD4+ cells, and Tregs can all be activated. Hence there is some risk for significant toxicity (cytokine release syndrome) and T cell suppression. BiTE therapy has been approved in various hematological malignancies including leukemia, lymphoma and myeloma.

2) Immune mobilizing monoclonal TCRs (ImmTACs): Immune-mobilizing monoclonal TCRs against cancer (ImmTACs) are like BiTEs in the sense that they aim to link T cells and specific target antigens. Unlike BiTEs, however, they utilize an HLA-A dependent sys-

tem. ImmTACs combine an engineered MHC class 1 molecule on one end and a single-chain variable region on the other end. The most clinically advanced example is the recently FDA-approved tebentafusp, an HLA-A 02:01 restricted agent targeting the melanocytic antigen gp100 with a CD3 variable chain fragment. This agent has demonstrated efficacy in clinical trials of patients with metastatic uveal melanomas.

Oncolytic Viruses

Oncolytic viruses mediate antitumor effects in several ways. Viruses can be engineered to efficiently infect cancer cells preferentially over normal cells, to promote presentation of tumor-associated antigens, to activate "danger signals" that promote a less immune-tolerant tumor microenvironment, and to serve as transduction vehicles for expression of immune modulatory cytokines. Talimogene laherparepvec (T-VEC) utilizes an attenuated herpes simplex virus 1 virus to overexpress granulocyte macrophage colony-stimulating factor (GM-CSF), which promotes dendritic cell-mediated antigen presentation. T-VEC improved durable response rates (compared with intratumoral GM-CSF alone) in patients with unresectable, injectable advanced melanoma. This agent was approved by the FDA for patients with unresectable or advanced melanoma who have an injectable skin or lymph node metastasis but limited visceral disease. It is being actively investigated in various trials in combination with other immunotherapies.

Therapies targeting other cell types in the tumor microenvironment

Targeting various inhibitory molecules (Killer Immunoglobulin-like Receptor for NK cells and Colony Stimulating Factor CSF-1R for macrophages) has been successful in various cancers. Pexidartinib has regulatory approval for the treatment of unresectable tenosynovial giant cell tumor, a locally aggressive neoplasm that overexpresses CSF-1R.

Vaccines

There is a long history of attempting to use vaccines to harness the adaptive immune recognition of a cancer-related antigen to effect antitumor responses. Antigen choices range from simple peptides all the way to whole-cell preparations that offer a broader range of antigens but are more costly and time-consuming to prepare. The only approved vaccine-based therapy for advanced cancer is sipuleucel-T, which is an autologous dendritic-cell preparation engineered to target prostatic acid phosphatase (PAP). This antitumor vaccine demonstrated an overall survival benefit in men with castrate-resistant prostate adenocarcinoma. Currently, various vaccines are being studied for lung, pancreatic, colorectal, melanoma, brain, and kidney cancers.

Predictors for response to Immunotherapy

Various predictive markers from the biopsy specimen are used including PDL-1 expression in the tumor, tumor mutation burden and tumor infiltrating lymphocytes to predict response to immunotherapy.

In conclusion, immunotherapies persistently re-engage and re-ignite the immune system in the fight against cancer, at times overcoming tumors which in the past have resisted multiple lines of chemotherapy. This is an exciting era for cancer researchers, since immunotherapies have shown to reduce mortality and improve survival. In addition, immunotherapies often have fewer side effects, translating to better quality of life while on therapy. As more and more cancers are shown to respond to immunotherapy, medical oncologists appear to be entering a new age in their battle against the ravages of malignant disease.

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Dr. Praveen Tumula chose to be a physician after seeing his father's commitment and dedication to serve patients. He graduated from medical school in India, and wanted to be an oncologist after he lost his grandfather to lung cancer. After one year of dedicated research in lung cancer at MD Anderson Thoracic Oncology, he went on to a residency at Hackensack Mountainside Hospital in NJ and a fellowship in Hematology Oncology at Boston University. He chose to work at Texas Oncology (part of the largest community oncology network in US) because it has given him access to various clinical trials and opportunities to collaborate with oncologists across the country. Being in the Panhandle has given him the opportunity to bring excellent care to the patients close to their homes.

Targeted Therapy: "The Chemo Pill"

by Leonardo Forero, MD

Introduction

Over 18 million people were diagnosed with cancer worldwide in the past year. 1 in 3 people will receive a cancer diagnosis in their lifetime. With over half a million cancer-related deaths in the US and 10 million deaths worldwide every year, it is surprising how few Americans are aware of the momentous steps taking place in cancer treatment in the US today. To better understand these recent developments, I will review new insights, approaches and therapeutic agents that I have witnessed develop during my career, from my fellowship at the UTHSA Institute of Drug Development to my current practice at Texas Oncology and the Veterans Affairs Medical Center (VAMC) in Amarillo.

"Do no harm": this axiom of medical practice is the most challenging objective for oncologists. Until 20 years ago, the only tool in our therapeutic cancer arsenal was chemotherapy. First generation chemotherapy was developed by the U.S. Army from several chemicals related to mustard gas, an agent that produced toxic changes in the bone marrow cells of soldiers exposed during World War II. This agent served as a model for a long series of similar but more effective agents (called alkylating agents) that kill rapidly growing cancer cells by damaging their DNA.

Hypotheses developed to explain the biological effects of mustard gas exposure led Dr. Alfred Gilman and Dr. Louis Goodman at Yale University School of Medicine to use nitrogen mustard to shrink the tumor masses in a patient with non-Hodgkin lymphoma. Since this 1943 breakthrough, many chemical derivatives have been formulated as chemotherapeutic agents, but their method remains the same: target and kill rapidly dividing cells. Though this was an unprecedented step forward in cancer treatment, chemotherapy's inability to differentiate between proliferating cells in healthy versus cancerous tissue gives rise to significant toxicities. The non-specific nature of chemotherapy also limits its applicability in older patients with poor or borderline performance status or multiple comorbidities.

In recent years, we have taken another dramatic leap forward in our ability to fight cancer – this time, by developing drugs that act on specific targets involved in the proliferation and differentiation of cancer cells, while causing minimal toxicity to normal cells.

Cancer results from the accumulation of genetic damage (somatic mutations) on genes that control differentiation and proliferation arising from a single normal cell. This rogue cell becomes the progenitor of a group of cells that share its abnormal capabilities, with later clinical manifestations. Until this point, the explanation of the cancer origin is simple and straightforward. The most difficult and confusing part for non-specialists, though, will be to deal with concepts like driver or actionable mutations, p53-mediated apoptosis, downstream signaling pathways, oncogenes, RTK/RAS/MAP-kinase pathway, and tumor suppressor genes, just to mention few. For simplicity I will focus this article on tyrosine kinase inhibitors (TKIs) for treatment of solid tumors.

Targeted therapy: a case study

One of my early and significant applications of therapeutic agents to replace chemotherapy was with Gwen, a lovely American/Vietnamese lady. She came to my office complaining of shortness of breath produced by a large malignant pleural effusion associated with a left pulmonary mass. Pathology confirmed diagnosis of malignancy: non-small cell carcinoma, adenocarcinoma subtype. As I read through her pathology report, I prepared the usual protocol that I would relay to her – the same outlook and limited options that I've had to give to many patients in her situation. Chemotherapy would definitively be difficult to tolerate for someone of her age. As I continued interviewing her, with the words "hospice" and "pain management" floating in my mind, two facts about her case caught my attention, rerouting my train of thought entirely. Gwen was Asian, and a nonsmoker. These key factors were valuable clues that Gwen might have a mutation of the epidermal growth factor receptor (EGFR) gene, one of the only mutations for which, at the time, a revolutionary biological cancer treatment had been developed and approved. For the first time, I was preparing to greet the worst stage of the deadliest cancer with an actual "targeted" fight. One of the first approved forms of targeted therapy for cancer using a tyrosine kinase inhibitor (TKI) of the EGFR type had been developed. This drug changed the outlook for Gwen, and eventually changed the way we treat cancer across the board. The first steps toward outgrowing the primitive and poisonous nature of chemotherapy had been taken.

The most successful type of molecular targeted therapy for cancer treatment involves small molecule inhibitors (SMIs) that target only proteins or enzymes coded by the genes carrying a particluar mutation in cancer cells. The most successful of these (and the example I will use to illustrate the life changing developments being made) are tyrosine kinase inhibitors (TKIs) for solid tumors.

When I learned that Gwen was an Asian nonsmoker, I immediately thought

of erlotinib, a first generation TKI that had been approved in 2004 for non-small cell lung cancer. It is common for non-smoking lung cancer patients to have a mutation in the epidermal growth factor receptor (EGFR), the mutation that erlotinib was designed to jam. Moreover, EGFR-sensitizing mutations occur in 45.7% of Asian patients with lung adenocarcinoma, as opposed to 17.3% of Western patients. Mutational analysis for an actionable mutation (a mutation with a matching drug designed to restore a normal signaling pathway) was the next diagnostic procedure. The molecular analysis came back positive for an EGFR sensitizing mutation (L858R). Gwen became a candidate for an oral tyrosine inhibitor of the epidermal factor receptor – or a "chemo pill", as she calls it.

Tyrosine Kinase inhibitors (TKIs)

Oncogenic mutations involving upstream tyrosine kinases lead to constitutive (always turned-on) and unregulated signals for the cell to grow and keep growing. At least 58 receptor tyrosine kinases (RTKs) and 32 non-receptor tyrosine kinases (NRTKs) have been found so far. These receptors have an enzymatic function that catalyzes the transfer of a phosphoryl group to tyrosine residues on their protein substrates, thus triggering the activation of the downstream signaling cascade.

A tyrosine kinase inhibitor (TKI) is designed to inhibit its kinase from playing the usual role of catalyzing phosphorylation. An analogy I use with my patients is: imagine an electrical lighting system. A mutation in the light switch (RTK) will leave the light permanently "ON". A "blocker" in the wiring (TKI) will turn off the signal or light. Whereas chemotherapy targets rapidly dividing cells and seeks to kill them, SMIs such as EGFR-TKIs penetrate the cell membrane and bind to a specific enzyme in the signal transduction pathway, thus halting the division of cancer cells from within. EGFR-TKIs are one of ten TKIs available for use today.

Gwen had an almost complete response to erlotinib initially, without any toxicity, allowing her to return to her normal daily activities. However, three years after starting on erlotinib, she developed a nonproductive cough associated with a new hilar mass, consistent with disease progression. Biopsy with mutational analysis confirmed the development of a resistant mutation that allowed growth signals to bypass the first-generation inhibitor. Fortunately, by this time, second and third generation EGFR-TKIs had already been approved for treatment of lung adenocarcinoma. I prescribed Gwen a third generation EGFR-TKI called osimertinib in May of 2018. Osimertinib is an irreversible TKI, making a covalent bond to the corresponding kinase, thus inhibiting the phosphorylation and activation of the downstream signaling cascade more effectively.

I last saw Gwen, now 80-years-old, on December 30, 2021. She's been taking

| *continued on page 14*

osimertinib since switching over in 2018 and is currently symptom-free seven years after being diagnosed with stage IV pulmonary adenocarcinoma. This is a dramatically different prognosis and quality of life than my patients with the same diagnosis and stage faced when I started my fellowship.

Challenges

Even though the number of new FDA approved indications for targeted agents keeps growing, the percentage of tumors carrying an actionable mutation amenable to TKI inhibition is still less than 20 percent of total lung malignancies. Another very important obstacle is the lack of adequate cancer tissue for molecular testing. About 20 percent of non-small cell pulmonary carcinoma patients in academic centers lack adequate tissue for testing. There are many reasons for this, but the main reason is that the tissue just gets used up. The more approved drugs for actionable mutations and combination of drugs for resistant mutations we have, the more tissue is needed for molecular analysis. Gwen's tissue samples from 7 years ago may not even have been studied for mutations that are be actionable today. Newly developed cell free DNA plasma/blood tests or "liquid biopsies" promise to help to solve this emerging problem.

Conclusion

Targeted agents are superior to traditional chemotherapeutic ones in selectivity, efficacy, and safety by acting on specific targets involved in cancer pathways with minimal toxicity to normal cells. At present, targeted therapies have been developed for lung cancer, colorectal cancer, head and neck cancer, breast cancer, multiple myeloma, lymphoma, prostate cancer, pancreatic cancer, melanoma and more. The most significant "toxicity", paradoxically, is a non-physiologic one, and yes, I'm talking about the financial one. Cancer patients are 2.5 times more likely to file for bankruptcy after they are diagnosed, according to the Fred Hutchinson Institute for Cancer Outcomes. The monthly cost of each new TKI is conservatively estimated to be between 8 to 15 thousand dollars, and, if the development of new or combination drugs keeps its current trend, the obvious exacerbation of the financial toxicity remains. There is currently no clear solution for this unsustainable system.

Dr. Leonardo Forero grew up in Bogota, Colombia and received his medical degree from Colegio Mayor de Nuestra Senora del Rosario University. He served as a research fellow in Immunology, then completed his internship and residency in internal medicine in Dallas at UT Southwestern Medical School and St. Paul University Hospital. He trained as a medical oncologist with emphasis in developmental therapeutics (Phase I clinical trials) at UT Health Science Center at San Antonio. Currently he is the principal investigator for Texas Oncology West Region Developmental Therapeutics clinical trials. Dr. Forero has presented, authored and co-authored a number of scientific articles in peer-reviewed medical journals and has presented at numerous scientific meetings.

PANHANDLE HEALTH

A Publication of the Potter-Randall County Medical Society

Editorial Policy and Information for Authors

Purpose *Panhandle Health* strives to promote the health and welfare of the residents of Amarillo and the Texas Panhandle through the publication of practical informative papers on topics of general interest to most physicians while maintaining editorial integrity and newsworthiness.

Spectrum *The Journal* seeks a wide range of review articles and original observations addressing clinical and non-clinical, social and public health, aspects as they relate to the advancement of the state of health in the Texas Panhandle. Pertinent letters to the editor, news submissions, and obituaries listings are accepted pending editorial review. The Editorial Board accepts or rejects submissions based on merit, appropriateness, and space availability.

Submission process Material should be e-mailed to the editor at prcms@suddenlinkmail.com or mail a hard copy to Cindy Barnard, PRCMS, 1721 Hagy, Amarillo, TX 79106. A recent photograph of the author (optional) and a curriculum vitae or a biographical summary are also to be submitted.

Conflict of Interest Authors must disclose any conflict of interest that may exist in relation to their submissions.

Journal Articles Manuscripts should be double-spaced with ample margins. Text should be narrative with complete sentences and logical subheadings. The word count accepted is generally 1200 to 1500 words. Review articles and original contributions should be accompanied by an abstract of no more than 150 words.

References References to scientific publications should be listed in numerical order at the end of the article with reference numbers placed in parentheses at appropriate points in text. The minimum acceptable data include:

Journals: Authors, article title, journal, year volume, issue number, inclusive pages.

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Pancreatic Cancer

by Shane Holloway, MD

Pancreatic cancer (adenocarcinoma) remains one of the most lethal malignancies in the United States. Despite considerable progress in the treatment of most solid malignancies, little progress has been made in improving survival for pancreatic cancer over the last 50 years. There were an estimated 60,430 new cases of pancreatic cancer in 2021, making up 3.2% of all new cancer cases. Pancreatic cancer occurs at a slightly higher rate in men (53% vs 47% in women). For 2021 the SEER database estimates there were 48,222 deaths from pancreatic cancer, accounting for 7.9% of all cancer deaths. The median age at diagnosis in the United States is 70 years of age, and the median age at death is 72 years of age (1).

Survival for pancreatic cancer, like many other solid malignancies, is dependent on stage. Pancreatic cancer staging has been established by the American Joint Committee on Cancer. The common elements of staging include four main factors: 1) location of the primary tumor, 2) tumors size and extent, 3) lymph node involvement, and 4) presence or absence of distant metastasis. Overall survival is highly dependent on the presence or absence of lymph node involvement. For stage I and IIa, where there is no nodal involvement, 5-year survival is 39%. Stage IIb and III survival is 13%, and stage IV survival is 3%. (ACS and AJCC survival data). Unfortunately, 85% of patients present with either stage IV disease or inoperable tumors. Only 11% present with stage I or IIa disease (4).

Screening for pancreatic cancer: problems and recommendations

90% of all cases of pancreatic cancer are sporadic, while 10% are hereditary. Developing a screening modality that allows the early detection of pancreatic cancer would improve outcomes by allowing diagnosis at an earlier stage. Currently, there are no cost-effective tests with adequate sensitivity or specificity to screen the general population. The International Cancer of Pancreas Screening Consortium recommends that screening not be performed on a population basis but in groups that are deemed high risk. Those at high risk include individuals in families with inherited risk, people with cystic lesions of the pancreas, and people older than 50 with newly diagnosed type 2 diabetes. Smoking is the most important modifiable risk factor, with 25% of those diagnosed having a significant smoking history. Obesity is the second most common modifiable risk factor, with those having a BMI >30 being 20% more likely to develop pancreatic cancer over their lifetimes (2). Known genetic mutations associated with pancreatic cancer include the *p16* mutation associated with familial atypical multiple mole melanoma (FAMMM), the *APC* gene mutation associated with familial adenomatous polyposis (FAP), *BRCA1* and *BRCA2* mutations, hereditary nonpolyposis colon cancer (HNPCC), Peutz-Jeghers syndrome, and the *ATM* gene mutation associated with ataxia telangiectasia. In these patients, and any others with 2 first degree relatives diagnosed with pancreatic cancer, screening is recommended. There is no consensus as to whether screening should start at the age of 40 or 50, but there is agreement that Endoscopic Ultrasound (EUS) and/or MRI are the best modalities for screening (4).

Clinical presentation and staging

The peak incidence of pancreatic cancer is between 60 and 80 years of age. The symptoms are insidious in onset and gradually progress over time. The most common symptoms experienced are midepigastric pain (frequently radiating to the back), weight loss, early satiety, nausea, and jaundice. A patient in this age group who presents with these symptoms should undergo initial computed tomography (CT) with intravenous contrast.

Once pancreatic cancer is suspected, a multidisciplinary consultation is recommended. This includes expertise from diagnostic imaging, interventional gastroenterology, medical oncology, radiation oncology, and surgical oncology. Locally, evaluation is best facilitated by referral to surgical oncology, medical oncology, or interventional gastroenterology. Patients found to have a pancreatic mass on CT imaging will undergo endoscopic ultrasound (EUS) to allow biopsy, biliary stenting if obstruction is present, and assessment of whether the lesion is operable. Once the diagnosis of pancreatic cancer is confirmed by biopsy, PET/CT is usually obtained to complete staging. After initial staging studies have been performed, patients can be divided into 4 categories: 1) Resectable, without metastatic disease, and no invasion of the portal vein (PV), superior mesenteric vein (SMV), superior mesenteric artery (SMA), celiac artery (CA), or hepatic artery (HA). 2) Borderline resectable, which means involvement of the vascular structures but operable with vascular resections and reconstruction. 3) Locally advanced with extensive vascular involvement precluding resection. 4) Metastatic.

Surgical management

Treatment, in the United States, should follow the National Comprehensive Cancer Network (NCCN) Guidelines. These are published online and via an app accessible to providers, and also include a patient portal where patients can view current treat-

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ment recommendations. Patients with resectable disease and no high-risk features should proceed to diagnostic laparoscopy and surgical resection, followed by adjuvant chemotherapy. High-risk features include highly elevated CA 19-9, large tumors, large regional lymph nodes, excessive weight loss, and extreme pain. If high risk features are present, the NCCN recommends neoadjuvant chemotherapy. Although these are generally accepted guidelines, the management of patients with resectable disease (both low-risk and high-risk patients) is still in flux, pending the outcome of several ongoing clinical trials.

Individuals with borderline resectable tumors (i.e., with vascular involvement as mentioned above) should receive neoadjuvant chemotherapy. After neoadjuvant therapy and repeat staging with CT, those with no evidence of metastatic disease or progression should then undergo diagnostic laparoscopy and surgical resection (often with postoperative adjuvant therapy). Those patients with locally advanced disease should undergo chemotherapy followed by chemoradiation or stereotactic body radiation (SBRT). They can undergo repeat imaging and consideration of resection, if feasible, or continue with systemic therapy if not feasible. Patients with metastatic disease with a good performance status will receive chemotherapy or chemoradiation if not candidates for aggressive chemotherapy. Those with poor performance status should be evaluated by palliative care.

The surgical procedure for pancreatic cancer depends on the location of the tumor within the pancreas. All patients undergoing resection should have diagnostic laparoscopy to rule out microscopic peritoneal disease, not detectable on preoperative imaging, which would preclude resection. Tumors located in the pancreatic head require a pancreaticoduodenectomy (also known as Whipple procedure), for surgical resection. Traditionally a Whipple is an open procedure taking an average of 6.4 hours in a recent meta-analysis. With advances in minimally invasive surgery, select institutions have begun using the DaVinci robot system to perform pancreaticoduodenectomies with mean operative times of 7 hours. Studies thus far have shown decreased blood loss, shortened length of stay, and similar perioperative complications, while data is still lacking to compare the oncological outcomes (3). Tumors located in the pancreatic body and tail are managed with distal pancreatectomy via open, laparoscopic, and robotic approaches. Open versus minimally invasive approaches for this procedure have similar outcomes in terms of operative times, complications, and oncologic outcomes, with decreased length of stay and blood loss in the minimally-invasive group.

Treatment of extensive disease

The most effective chemotherapy regimen thus far for pancreatic adenocarcinoma, in both the adjuvant and neoadjuvant setting, for patients with a good performance status is a combination of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX). A second regimen consisting of gemcitabine and Abraxane (albumin-bound paclitaxel) has been found to have similar overall survival with slightly lower partial response rates but less toxicity. Those with poor functional status or advanced age are treated with either single agent gemcitabine or 5-fluorouracil (2).

The NCCN recommends that all patients with pancreatic cancer be tested for germline mutations using comprehensive gene panels for hereditary cancer syndromes. The most commonly used test is produced by Myriad Genetics. Gene profiling of tumor tissue is also frequently used, as there continues to be an ever-expanding list of targeted therapies available including those for *BRAF, KRAS, PALB2*, and *HER2* mutations. This testing will often give oncologists treatment options for patients with metastatic disease who have failed first- and second-line therapies or cannot tolerate cytotoxic therapies (2).

Pancreatic cancer remains a dismal diagnosis, with very few real advances in outcomes over the last 30 years. Despite surgical advances and new oncological treatments, very few patients achieve cure. Future efforts will continue to search for better early diagnostic tests including novel biomarkers, as well as technology that allows us to determine an individual's tumor phenotype and to develop treatment specific to their cancer.

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The RACE Act: *Expanding Options in Pediatric Cancer Treatment*

by Jeff Hanrahan, MD

HELLO AMARILLO!! As the new pediatric/young adult hematologist/oncologist at BSA/Harrington Cancer Center, I want to start off by saying that I am delighted to be here in Amarillo, and I am excited to help expand all medical services we provide to children and young adults in the Amarillo community, especially with respect to hematologic and oncologic needs. As part of this expansion, I very much look forward to improving the participation in, and enrollment of, children and young adults in cooperative group clinical trials (such as the Southwest Oncology Group or SWOG) and/or pharmaceutical sponsored clinical trials. As other articles in this issue demonstrate, scientific advances have allowed the development of molecularly- targeted drugs in hematology and oncology, further advancing the concept of precision medicine. Thankfully, cooperative groups and pharmaceutical sponsors have recognized this concept! They are now working together as never before to bring to clinical trial new molecularly-targeted hematology and oncology treatments for both pediatric and adult patients. Such collaboration, I know, will ultimately lead to improved outcomes and diminishing toxicity in the treatment of malignant disease in young persons.

In furtherance of the above, one exciting, recent, and much-needed piece of legislation has been the enactment of The Research to Accelerate Cures and Equity (RACE) for Children Act. Commonly known as the RACE act, it aims to improve and expand treatment options for pediatric and young adult cancer patients by mandating that all new adult oncology drugs also be tested in children, whenever the molecular targets are relevant to a particular childhood/young adult cancer. The RACE act was originally enacted in late 2017 under the Food and Drug Administration Reauthorization Act (FDARA), but was recently amended in August 2020.

The August 2020 amendment now requires that any original, new drug application or biologics license application submitted to the FDA after August 18, 2020 for a new active ingredient must contain reports of molecularly-targeted pediatric cancer investigations (unless a deferral or waiver of that requirement is granted) if the drug is:

* Intended for the treatment of an adult cancer, and
* Directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of pediatric cancer.

Of note, this pediatric investigation requirement applies EVEN IF the adult cancer indication does not occur in the pediatric population and the drug is for an adult indication for which orphan drug designation has been granted. Prior to the RACE act, the pediatric study plans for oncology drugs were generally proposals to request waivers for pediatric assessments because the adult cancer indications for which a drug was developed did not occur or occurred only rarely in pediatric patients, making pediatric studies impossible or highly impracticable.

In past years, the advances seen in the treatment of an adult oncology indications had rarely been extended to pediatric cancer treatments. Fortunately, much research now has demonstrated that malignancies occurring in children, adolescents and young adults can harbor the same molecular abnormalities as those found in adult cancers, suggesting that the new targeted oncology drugs may prove effective in treating pediatric and younger adult patients with cancer, even if that particular adult cancer does not occur in the pediatric population. This is further supported by the fact that up to 50% of pediatric cancers harbor a

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molecular target that can potentially be addressed by a targeted drug already approved in adults.

LEGISLATIVE BACKGROUND

Interestingly, Congress and the FDA have previously passed legislation and created policies to encourage pediatric drug development, including but not limited to, oncology drugs. The Best Pharmaceuticals for Children Act of 2002 (BPCA) provided the incentive of additional marketing exclusivity to pharmaceutical sponsors who voluntarily complete certain pediatric clinical studies requested by the FDA. These studies were enumerated in the Pediatric Research Equity Act (PREA) of 2003. The PREA authorizes the FDA to require drug manufacturers to complete studies in children for the same adult indications whenever the drugs are expected to be used in a substantial number of children.

Specifically, the PREA requires submission of an initial pediatric study plan (iPSP) prior to the commencement of Phase 3 studies for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration for a particular drug or biologic. The iPSP should contain an assessment of safety and effectiveness of the investigational drug for the proposed indication in all relevant pediatric subpopulations. In certain situations, a deferral or waiver for conducting pediatric studies can be obtained. After August 2020, all sponsors of new adult molecularly-targeted cancer drugs must submit an iPSP for potential pediatric use.

The PREA does not apply to any drug application for an indication for which orphan drug designation has been granted when that application would otherwise trigger PREA. However, FDARA, in furtherance of the RACE act, has eliminated the orphan drug exemption for pediatric cancer drugs directed at relevant molecular targets.

RELEVANT (AND NONRELEVANT) MOLECULAR TARGETS

In collaboration with the government, academic and industry experts and advocates, the FDA has worked to establish guidance to pharmaceutical sponsors by publishing two lists:

- Relevant molecular targets considered to be substantially relevant to the growth or progression of pediatric cancer
- Nonrelevant molecular targets that warrant waiver from required evaluation because they are not substantially relevant to the growth or progression of pediatric cancer

These lists are intended as guides to sponsors as they consider development plans for new targeted drugs and early pediatric assessments. Moreover, sponsors of molecularly-targeted oncology drugs are encouraged to seek early advice and guidance from the FDA in determining relevance and non-relevance.

iPSP CONTENT

By way of example, the FDA expects an iPSP for a new adult molecularly-targeted oncology drug to include the following elements:

* Description of the cancer(s) in the pediatric population for which the drug warrants early evaluation
* Overview of the drug product
* Overview of the planned extrapolation of effectiveness to the pediatric population
* Planned request for drug-specific wavers and partial waivers, with justification
* Planned request for deferrals of pediatric studies
* Tabular summary of proposed non-clinical and clinical studies
* Age-appropriate formulation including details of existing or planned excipients
* Non-clinical proof-of-concept studies
* Data to support clinical studies in pediatric patients
* Planned pediatric clinical study or studies
* Timeline of the pediatric development plan
* Agreements for pediatric studies with other regulatory agencies

CONSIDERATIONS FOR RARE CANCERS

The FDA also allows for options in situations where the scarcity of affected pediatric patients precludes the use of conventional studies, such as embedding a pediatric cohort in an existing trial, including adolescent patients by lowering the age requirement for enrollment, considering tissue and histology agnostic clinical trial development (which would allow enrollment of multiple pediatric cancers with shared genetic abnormalities), or using master protocols such a umbrella or basket trial designs.

DEFFERALS AND WAIVERS

Deferral of the pediatric study may be appropriate until sufficient evidence of clinical activity is observed in response to the inhibition of a defined molecular target or pathway, when there is uncertainty regarding the single agent activity of a drug, or until appropriate pediatric formulation is available, provided there has been due diligence in formulation development

Finally, on a personal note, since being in Amarillo, I have already utilized new molecularly-targeted therapies originally developed for adults on a few of my pediatric/young adult patients who have not responded to of have relapsed after first-line therapy. I firmly believe that the RACE act will provide valuable incentive to increase the development and application of newer therapies for my patient population, and I am excited to participate in these new clinical trials locally. I look forward to sharing more information with my new medical colleagues and friends here in Amarillo as we continue to provide quality care to our patients. Finally, I would like to thank everyone here for being so warm and gracious in welcoming me to the Yellow City!

Jeff Hanrahan attended medical school at St. George's University School of Medicine. He completed his internship and a Fellowship at the University of New Mexico. Dr. Hanrahan specializes in the diagnosis and treatment of all pediatric cancers and blood disorders. He is currently associated with the BSA Harrington Cancer Center.

Advances in the Management of Lung Cancer

by Tucker Osteen, MD

Certain things about lung cancer remain true from one generation to the next: it is insidious, often aggressive, and challenging to treat. According to the National Cancer Database, lung cancer remains the second most common cancer diagnosed in women in the United States (behind breast cancer). Lung cancer remains the second most common cancer diagnosed in men in the United States (behind prostate cancer). In the United States in 2018, there were 219,000 patients with a new lung cancer diagnosis. The prognosis of lung cancer continues to remain poor. In the United States, lung cancer has the highest death rate of all malignancies. In 2018 there were 142,000 cancer deaths attributed to lung cancer. This disease still affects tobacco smokers much more than non-smokers. Patients often present with advanced-stage disease which tends to make curing this cancer even more of a challenge.

The two categories of lung cancer are small-cell lung cancer and non-small-cell lung cancer. Both categories carry a poor prognosis and a common organ of origin. Beyond these characteristics, however, they are very different diseases. The malignant cells differ microscopically, the staging of these two cancers is different, the natural course of the disease is different, and the therapies are different.

Non-small cell lung cancer: Local and regional disease

Approximately 85% of lung cancer in America is non-small-cell lung cancer, which is further subdivided based on the cell of origin in the lung. The most common subtypes are adenocarcinoma, which makes up about 50% of all lung cancers, and squamous cell carcinoma, which makes up about 30% of all lung cancers.

Non-small-cell lung cancers, in general, tend to metastasize more slowly than small-cell carcinoma. This leads to more frequent diagnosis with earlier-stage disease.

A primary tumor in one lobe of the lung without lymph node involvement defines stage I non-small-cell lung cancer. In contrast, a primary tumor and local lymph nodes within a single lung lobe define Stage II disease. The primary treatment of stage I and II disease is a lobectomy or stereotactic body radiation therapy. This procedure can be curative. To increase the chance of cure in stage II non-small-cell lung cancer, patients receive systemic treatment, often chemotherapy, after surgery.

Stage III disease gets treated with a combination of chemotherapy, immunotherapy, radiation therapy, and surgery. A stage III cancer patient receives neoadjuvant therapy, such as chemotherapy or chemotherapy together with radiation, before surgery with the goal of increasing the chance of a cure. When a patient undergoes surgery without neoadjuvant therapy, the patient receives adjuvant therapy, which is chemotherapy administered after surgery with the goal of increasing the cure rate. Studies going back to the 1990s show that patients with stage II or stage III non-small-cell lung cancer who received platinum-based doublet chemotherapy plus or minus radiation along with the surgery have approximately 5% better survival rate than patients having surgery alone.

Many patients with stage III disease, however, are not surgical candidates. The best treatment for these patients is concurrent chemotherapy and radiation therapy, followed by consolidation immunotherapy with durvalumab (Imfinzi). The Pacific trial patients gained 10% in overall survival when durvalumab was added (1).

Targeted therapies have changed the practice of oncology. Tumor testing often reveals driver mutations, with drugs designed to target many of these mutations. While treatment of metastatic non-small cell lung cancer has benefited dramatically from these new agents (see below), targeted therapies are starting to show benefit in the adjuvant setting as well. For instance, in one recent study, patients with an EGFR driver mutation were randomized to receive adjuvant therapy with a drug that targets EGFR called osimertinib (Tagrisso) versus placebo. Disease free survival improved significantly for patients with stage II or stage III disease. At 36 months, 20% of the patients receiving osimertinib had relapsed disease, as compared to a 72% recurrence rate at 36 months in the placebo arm (2).

Metastatic non-small cell lung cancer

In the last few years, targeted therapy and immunotherapy have changed our entire approach to treating patients with stage IV metastatic non-small cell lung cancer. Tumors should routinely be tested for driver mutations and programmed death-ligand 1 (PD-L1) status. Patients in the non-squamous category of non-small cell lung cancer are particularly likely to have potentially targetable mutations such

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as EGFR, ALK fusion, ROS-1 fusion, BRAF V600e, MET exon 14 splices, RET fusion, K-RAS, and HER-2. Patients with one of these mutations generally do not receive chemotherapy as a first-line treatment.

Targeted therapy

For example, patients diagnosed with metastatic non-squamous, non-small-cell lung cancer who are found to have an EGFR-activating mutation such as exon 19, L858R, and T790M receive treatment in the first-line with an EGFR tyrosine kinase inhibitor. This class of oral drugs includes osimertinib (Tagrisso), erlotinib (Tarceva), gefitinib (Iressa), and afatinib (Gilotrif). These drugs have proven more effective in the first-line setting than chemotherapy in multiple randomized clinical trials. First-line response rates to an EGFR tyrosine kinase inhibitor are approximately double the response to chemotherapy. There is also a significant increase in progression-free survival. For example, progression free survival of patients with an EGFR T7 90 M mutation is 10.1 months for patients treated with single-agent osimertinib compared to only 4.4 months in patients treated with platinum doublet chemotherapy (3). These findings have been stable over multiple trials, and in the setting of an EGFR mutation, a tyrosine kinase inhibitor is currently first-line standard of care.

There are similar findings for patients who have a positive ALK fusion. This fusion is the second most common mutation found in non-squamous non-small-cell lung cancer. ALK Inhibitors target this mutation; they are also oral medications. Examples include crizotinib (Xalkori), ceritinib (Zykadia), brigatinib (Alunbrig), alectinib (Alecensa), and lorlatinib (Lorbrena). Across multiple randomized clinical trials, this class of drugs is proven to be more effective than chemotherapy in the first-line and second-line settings. In one trial, ceritinib improved progression free survival in patients with an ALK fusion to 16.6 months, versus 8.1 months in patients treated with chemotherapy (4). In cases of metastatic non-squamous non-small cell lung cancer, ALK inhibitors are now the standard of care.

Phase 2 single-arm trials have also shown favorable outcomes with multiple other targeted therapy options, leading to FDA approval of many additional agents. Crizotinib (Xalcori) and entrectinib (Rozlytrek) have proven effective for patients with a ROS1 fusion. Dabrafenib (Tafinlar) and trametinib (Mekinist) have shown efficacy for patients with a BRAF *V600e* mutation. In addition, the FDA has approved selpercatini (Retevmo) and pralsetinib (Gavreto) for the treatment of patients with RET fusion, as well as capmatinib (Tabrecta) and tepotinib (Tepmetko) for the treatment of *MET* exon 14 splice mutations. Finally, drugs have recently been approved to treat EGFR exon 20 insertion mutations (amivantamb) and *K-ras* G12C mutations (sotorasib).

Patients with stage IV squamous cell carcinoma of the lung are unlikely to have targetable mutations. Unfortunately, there is not a role for targeted therapies in this subset of patients at this time.

Immunotherapy

The role of immunotherapy is dramatically increased in stage IV non-small cell lung cancer for patients with adenocarcinoma who do not have a targetable mutation and for all patients with squamous cell carcinoma. Immunotherapy with agents such as pembrolizumab (Keytruda), nivolumab (Opdivo), atezolizumab (Tecentriq), and cemiplimab (Libtayo) are approved in the first-line setting for adenocarcinoma patients without a targetable mutation and for all patients with squamous cell carcinoma. In general, the higher the PD-L1 score, the more likely a patient is to respond to immunotherapy. As a result, single-agent immunotherapy focuses on patients with higher PD-L1 scores. Combinations of immunotherapy and chemotherapy are usually the preferred treatment for patients with low PD-L1 levels. Pembrolizumab, for example, is approved for use as monotherapy in patients with PD-L1 scores greater than 1% and in combination with chemotherapy regardless of PD-L1 score. In the Keyote-042 trial, single agent pembrolizumab increased overall survival in this patient group to 16.7 months (compared to 12.1 months for chemotherapy alone) in patients with detectable PDL-1 (5). Nivolumab combined with ipilimumab (Yervoy) is approved for PD-L1 score greater than 1% or together with chemotherapy irrespective of PD-L1 score. Atezolizumab is approved for monotherapy if the PD-L1 score is greater than

50%; it is also approved in combination with chemotherapy regardless of the PD-L1 score. Cemiplimab is approved as monotherapy in patients with a PD-L1 score greater than 50%. Therefore, patients with non-small-cell lung cancer who do not have a targetable mutation really should be given immunotherapy plus or minus chemotherapy as first-line treatment unless they have a contraindication to immunotherapy.

Treatment strategies for non-small cell lung cancer have evolved dramatically over the last few years. Many cancer patients receive treatment tailored to their specific cancer, and many derive benefit from oral medications. As a result, more patients live longer with less disease burden.

Small cell lung cancer: a different story

Unfortunately, small-cell lung cancer treatment advances have lagged behind. Small cell lung cancer is a different disease entirely. Small cell lung cancer is an aggressive neuroendocrine tumor that starts in the lung. Small cell lung cancer makes up about 15% of the lung cancer diagnosis in America. Approximately 95% of patients diagnosed with small cell lung cancer are active tobacco users. These patients usually present with metastatic disease and significant comorbidities. Small cell lung cancer tends to metastasize early in the disease process. Because patients are much more likely to present with metastatic disease, the potential of cure is lower. Surgery's role diminishes significantly in patients with small cell lung cancer. Only the rare patient with limited-stage small cell cancer will benefit from radiation therapy.

Small cell lung cancer is staged in a different way. The disease is divided into limited-stage small cell lung cancer, where the cancer is contained within a single radiation port, and extensive-stage small cell lung cancer. The overall survival for limited-stage disease is less than two years. The overall survival for extensive-stage disease is less than one year.

For decades, the backbone of therapy has been combination platinum doublet chemotherapy--usually four cycles of cisplatin and etoposide. Small-cell lung cancer tends to be exquisitely sensitive to chemotherapy in the first-line setting. Unfortunately, the treatment response is not durable. Therefore, the decision to use a second-line therapy depends on the durability of the first treatment. Usually, platinum doublet chemotherapy is given again to patients who did not relapse after chemotherapy for six months. Patients relapsing earlier than six months are traditionally treated with a topotecan-based regimen.

There are currently no targeted treatments for small-cell lung cancer.

Recently, immunotherapy treatments atezolizumab and durvalumab were approved in the first-line setting along with combination platinum-based chemotherapy for small-cell lung cancer. The addition of atezolizumab to combination chemotherapy increased overall survival to 12.3 months (from 10.3 months in patients receiving chemotherapy alone) (6). The addition of durvalumab to chemotherapy increased overall survival to 13.0 months from 10.3 months in patients receiving chemotherapy alone (7). This is followed by maintenance immunotherapy.

There is a recent approval of a new second-line treatment for small-cell lung cancer in patients who relapsed less than six months from the original platinum-based treatment. Before this, the options for relapse earlier than six months were limited to either topotecan or a clinical trial. But now there is a third approved option, lurbinectedin (Zepzelca). In a single-arm phase 2 trial, this agent, used as second-line treatment, improved progression-free survival by 3-1/2 months (8), The FDA granted lubinectedin accelerated approval in 2020.

Lung cancer continues to be a prevalent disease in America with a very poor prognosis. However, over the last ten years, treatment landscapes for lung cancer have changed a great deal. More treatment options continue to emerge for non-small-cell lung cancer, including targeted therapies and immunotherapy. Advances in small-cell lung cancer have been slower and less dramatic, but some new treatment approaches are developing.

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Dr. Tucker Osteen grew up in Amarillo, TX. He obtained his undergraduate degree from Baylor University and, after teaching high school chemistry for several years, attended and graduated from Texas Tech University School of Medicine in Amarillo. He completed his residency in Internal Medicine and fellowship in Hematology and Oncology at Baylor University Medical Center in Dallas. Dr. Osteen returned home with his wife and three children to practice hematology and oncology in Amarillo.

Prostate Cancer Update

by David Wilhelm, MD

Prostate cancer remains a commonly diagnosed cancer. Outside of skin cancer, it is the most common malignancy in men, affecting 1 in 8 men in their lifetimes. According to 2021 SEER data from the National Cancer Institute, prostate cancer represents 13.1% of all new cancers, with 248,530 new diagnoses. Although the 5-year survival rate is 98%, it was responsible for an estimated 34,130 deaths or 5.6% of all cancer deaths. Prostate cancer is most frequently diagnosed between ages 64 to 74 with a median age at diagnosis of 67 and median age at death of 80. Most prostate cancer deaths result from metastatic castrate-resistant prostate cancer (mCRPC). Although this disease state remains incurable, there are several novel treatments that improve both oncologic outcomes and quality of life in this population. Due to the length constraints of this article, I will focus on areas of this topic that have had the most profound growth and change.

Advanced Prostate Cancer

After definitive initial treatment, men are followed with serial exams and PSAs. For men who have a PSA-only recurrence, this is termed biochemical recurrence. This is the area that has seen the biggest explosion in diagnostic and treatment options, both for men with recurrence and those who present initially with advanced disease. For decades the only method of treatment for progression after therapy was androgen blockade and the blockade of testosterone production. Prostate cancer is sensitive to testosterone, which stimulates cell growth for many prostate cancer cell lines. For men with treated disease and apparent good response, there is no indication to block testosterone; however, once there is concern for progression, this remains a mainstay of treatment. Charles Huggins won a Nobel Prize in 1966 for his work to identify the androgen pathway in prostate cancer in 1940. (As a trivia aside, only one other urologist, Werner Frossman, won a Nobel Prize. He worked as a urologist for most of his career, but early in his surgical training he invented procedures for cardiac catheterization and performed the first procedures on himself in 1929. This urologist won the Nobel Prize in 1956 for doing the first heart cath!).

Diagnostic Testing

Previously, diagnosis of metastatic disease was not possible until PSAs had climbed significantly; by that time CT and bone scan often showed numerous lesions. There were no better options for diagnosis at lower PSA levels. Now, though, we have PET/CT scanning for prostate cancer with F-18 fluciclovine (Axumin) scanning. This imaging is available in our community. Axumin imaging can detect and localize areas of recurrence at much lower levels of PSA. In a trial examining detection rates in men with various prior treatments, the detection rates were 40%, 60%, 72% and 85% for PSA levels of <0.79, 0.8-2.0, 2-6 and >6 (1). Modern imaging has identified metastatic and local recurrences sooner and has even allowed for treatment of local recurrences early with salvage therapy. Results are immature, but there is some hope this may avoid long term systemic therapy in select patients. There is an even newer PET/CT tracer, PSMA, that targets Prostate Specific Membrane Antigen. This imaging technique may move the needle even further down to PSAs of 0.2 for detection of recurrence. This is not readily available across the US at this time but moving into the main stream and will likely be available in our community soon.

Previously, many men were started on androgen deprivation prior to identification of metastatic disease based

on level of PSA or rate of PSA change (doubling time). This was with the knowledge that there was recurrence based on rising PSA levels, but due to limitations of diagnostic testing no disease was found. The advent of newer imaging techniques should change the landscape of treatment of recurrence, to allow for either directed therapy for localized recurrence or systemic therapy for more distant recurrence.

Recurrent disease

In the past many men were begun on androgen deprivation therapy (ADT) with medical therapy or surgical castration because of rising PSA despite castrate levels of testosterone. With conventional imaging, many of these men still had no evidence of disease. These men are categorized as non-metastatic Castrate Resistant Prostate Cancer(nmCRPC). For the sake of brevity, I will ignore this subset of the population as I think this is truly a misnomer and related to our lack of adequate imaging and diagnostic tools to classify these individuals as local or metastatic recurrence. As our technology continues to improve, I believe that this disease state will no longer exist. Ultimately, men will fall into categories of cure, locoregional recurrence or metastatic disease.

A review of trials of recently-approved drugs, however, will give some insight into the efficacy of treatment for men with early recurrence. There are now novel antiandrogens that block testosterone binding in the cancer cells as well as testosterone uptake into the cell nucleus. The concept is that, even though systemic testosterone has been blocked, the microenvironment of the tumor only needs very low levels of androgen (or may even produce its own androgen!) to allow cell growth. The SPARTAN trial showed a metastasis free survival (mFS) of 40.5 vs 16.2 months with apalutamide plus ADT vs placebo plus ADT (2). The PROSPER trial showed a similar mFS of 36.3 vs 14.7 months for enzalutamide vs traditional therapy (3). These trials showed improvement in all cohorts: time to PSA progression, progression free survival, time to symptomatic progression and time to subsequent therapy.

Metastatic prostate cancer

For those men with metastatic disease, the bedrock of therapy remains ADT. All the studies that have resulted in novel therapy were based on individuals already on ADT, and so all guidelines and therapeutic options require ADT as a starting point. Men who have metastatic disease despite ADT are said to have metastatic Castrate Resistant Prostate Cancer (mCRPC). The two drugs used in this space are abiaterone, a cytochrome P450 17 inhibitor that inhibits adrenal testosterone production, and enzalutamide, which is an antiandrogen. The PREVAIL trial showed overall survival (OS) of 35.3 vs 31.3 months for addition of enzalutamide to standard ADT (4). Abiaterone was shown in COU-AA-302 to have OS of 34.7 vs 30.3 months (5). Another agent that has been approved for men with minimally to asymptomatic metastatic disease is Sipucel-T. This is the first immunotherapy to show promise in the treatment of prostate cancer. It involves leukapheresis to extract the patient's white blood cells. Antigen-presenting cells are then programmed by exposing them to prostatic acid phosphatase antigen, and then these programmed T killer cells are reinfused into the patient. This is a series of 3 treatments done 2 weeks apart. The IMPACT trial showed a 4.1-month survival advantage and a 22% reduction in risk of death in treated patients. Follow up of this study showed an OS difference of 13 months for PSA <22.1, 7.1 months for PSA 22.1-50.1, 5.4 months for PSA 50.1–134.1, and 2.8 months for PSA > 134.1 (6). The one caveat to Sipucel-T therapy is that, despite differences in overall survival, there is not always a corresponding clinical, serological or radiographic response. Patients must be counselled about this in advance.

Chemotherapy is also available for men with mCRPC who have good performance status, especially those with higher volume disease. The TAX 327 trial showed an OS of 19.2 with docetaxel vs 16.5 months for mitoxantrone (7). The SWOG 9916 trials showed OS of 17.5 with docetaxel vs 15.6 months for mitoxantrone (8). Chemotherapy has traditionally been reserved for very advanced, high-volume disease. With the advent of newer imaging, men with higher volume disease (4 or more bony metastases or visceral metastasis) receive treatment earlier in the algorithm with better results, as would be expected with lower volume disease.

For men with minimally symptomatic bone metastasis, the radiopharmaceutical radium 223 has been shown to provide an OS benefit of 14.9 (vs 11.3 months) in the ALSYMPCA trial (9).

| *continued on page 24*

This is best sequenced prior to extensive chemotherapy, as bone marrow suppression will decrease the utility of radium. Another goal of bone therapy is minimizing bone density loss from prolonged hypogonadal state with bisphosphonates and RANKL antibodies such as denosumab. Both drug classes have been shown to decrease risk of bone density loss, but denosumab has also been shown to decrease risk of bone fracture. Men on prolonged therapy should be followed with bone density to assess need for treatment (other than calcium, vitamin D and weight bearing exercise). In men with bone metastasis, denosumab in a monthly dosing has been shown to decrease risk of first skeletal event by over 3 months.

Another promising radiopharmaceutical is PSMA-targeted lutetium 177. This is a beta-emitting radioligand attached to the PSMA tracer, which is then taken up in the prostate cancer cells. The benefits of beta emitting molecules are short maximal tissue penetration and long half-lives, providing more targeted therapy and higher radiation delivery to the targeted tissue. Although not widely available currently, this agent shows extremely impressive early results in trials of patient with high-volume metastatic disease.

Analysis of mismatch repair sequences (MMR) or germline alterations has revealed promising avenues for therapy in many cancers. Prostate cancer is no different. Men with high-risk disease or disease progression should be evaluated for germline mutations or MMR. In those men with MMR mutations, pembrolizumab has been shown to be effective and should be considered in these men. There is also a subset of men with BRCA mutations who can be treated with PARP inhibitors; initial studies have shown significant improvement in progression-free and overall survival with olaparib and rucarparib. These patients should be counselled about their risks of other malignancies and the risk to close relatives, as these germline mutations can be shared among family members.

The treatment landscape for men with recurrent or advanced prostate cancer has dramatically changed and continues to undergo an evolution. For many of these men, therapy continues to be directed by the urologist who initially diagnosed and treated their cancer. This has allowed continuity of care in an established environment. Many of these newer treatment algorithms are outpatient-based, with oral dos-

age forms and low morbidity. Optimal treatment relies on collaboration with our colleagues in radiology and medical oncology. I believe that, with continued improvement in diagnostic tools (both radiologic and genomic), the algorithm will continue to change. As in many other cancers, management will continue to be multimodal, and early identification of those who need intensified therapy is likely to minimize disease progression and death.

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Dr. David Wilhelm was born in Dallas, TX, attended undergraduate school at St. Louis University and graduated from medical school at Loyola University in Chicago. After completing a urology residency at University of Texas Southwestern, he joined Amarillo Urology Associates. He has been married to his wife, Lorraine, since medical school; they have four children. Dr. Wilhelm is an avid soccer fan.

Stereotactic Radiation Therapy

by Madhava Kanakamedela, MD

Stereotactic radiation treatment for several brain pathologies has resulted in better local control and fewer cognitive side effects than the traditional whole brain and partial brain radiation therapies.

Stereotaxis is the "accurate targeting technique for intracranial structures with high precision (Cartesian co-ordinates)," based on an external reference; traditionally, this has been frame-based. Lars Leksell pioneered the stereotactic head frame in 1948, initially for functional neurosurgery. Later, it was adapted for use in radiosurgery (Figures 1A-C). In the frame-based approach, fiducials in the localizer box that is attached to the frame act as external references for the intracranial structures while the frame provides rigid immobilization of the cranium.

With the advent of better imaging techniques and computational power, however, stereotaxis can now be achieved using the patient's skull as an external reference while the patient is firmly immobilized in a face mask (Figure 2). As the accuracy improves with number of fiducials in constant relation to the intracranial target, each point in the patient's skull can act as an independent fiducial in CT-based stereotactic localization. This enabled us to perform fractionated stereotactic radiation therapy (FSRT).

Traditionally, brain lesions ≤3 cm (≤10 cc) in size are amenable to single fraction stereotactic radiosurgery (SRS). If the lesion size is >3 cm, however, the integral dose to the brain is higher with the single fraction treatment, and these lesions are more safely treated with fractionated Stereotactic Radiation Therapy (SRT) in 2 to 5 fractions. For small lesions that are abutting critical normal structures (*e.g.*, optical structures, brainstem, cochlea), SRT is also the modality of choice (Table 1). The icon's flexibility in allowing for fractionated stereotactic treatments, as well as stereotactic radiosurgery, provides a complete intracranial solution to treating different sized lesions, even for those lesions abutting critical normal structures (1).

Fig. 1A. Stereotactic frame with 4 points of attachment to the skull.

Several dedicated machines for intracranial stereotactic radiosurgery/radiation therapy have been available, including cobalt-based Gamma Knife, miniaturized Linac on robotic arm (Cyberknife) and recently Zap-X. Even though these dedicated machines are justifiable for high volume centers, we are now able to deliver stereotactic treatments with Linac based radiosurgery.

Brain metastasis is the most common malignant tumor of the brain. Open craniotomy and excision are usually reserved for obtaining pathological diagnosis and for larger metastasis requiring immediate decompression. Initial randomized studies established SRS alone as the treatment of choice, for as many as 4 brain metastases. Recent literature and better planning algorithms have established safety even in patients with up to 10 brain metastases, as long as the total cumulative tumor volume less than 15 cc and the largest lesion is <3cm. (Figure 3).

Benign and atypical meningiomas that are in surgically inaccessible locations, recurrent lesions after surgery and meningiomas in medically inoperable patients can be treated with stereotactic radiation treatments. Again, fractionated stereotactic radiation therapy can be utilized for larger lesions > 3 cm in size or for those in close proximity to critical structures. (Figure 4)

Stereotactic radiotherapy used for the treatment of acoustic neuromas achieves high rates of tumor control

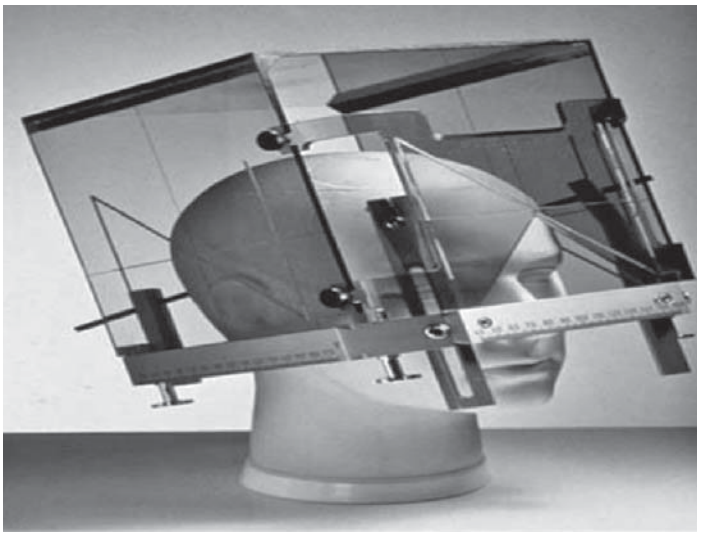

Fig. 1B. External localizer box attached to the stereotactic frame mounted on a phantom.

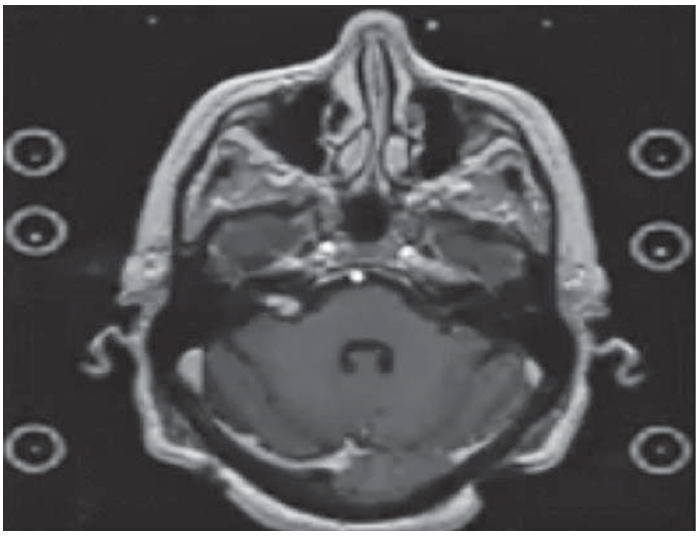

Fig. 1C. Fiducials from the localizer box are outlined in red circles on a representative MRI slice. Depending upon the location of each MRI slice, the location of the red circles will vary.

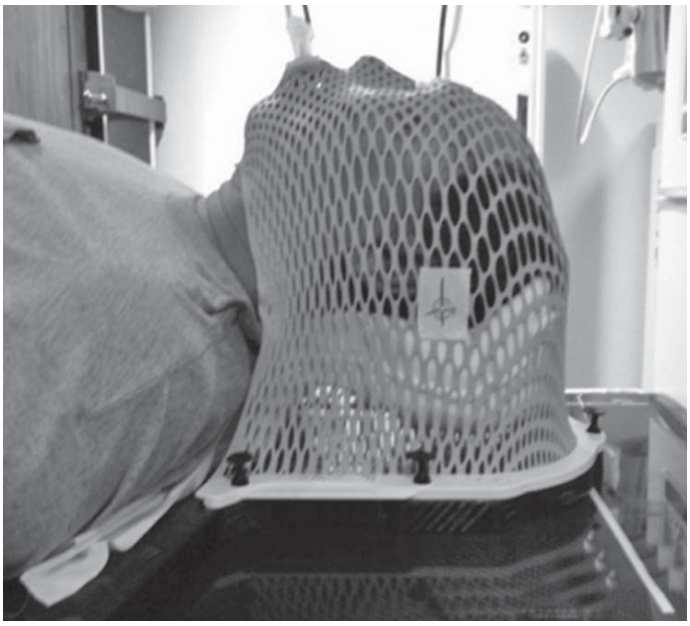

Fig 2. Patient is firmly immobilized in a face mask

Table 1 – Selection criteria for Frame versus Mask.

Frame	**Mask**
Invasive	Non-Invasive
Single Fraction SRS	Single Fraction SRS & Fractionated SRT
Ideal: Trigeminal, Acoustic & Pituitary	Not Ideal
Size: <3cm/<10 cc	Large lesions can be treated
Contraindicated for lesions abutting critical normal tissues (prescription doses > tolerance limits).	Fractionated treatment can be used for lesions abutting critical normal structures.

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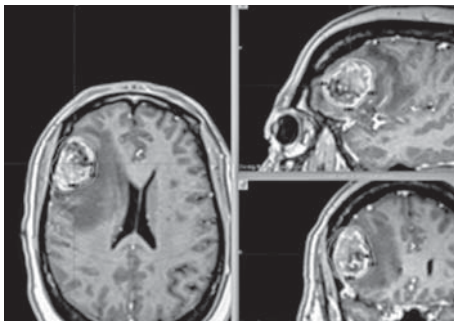

Fig. 3. Solitary brain metastasis from a breast cancer primary, treated with fractionated stereotactic therapy.

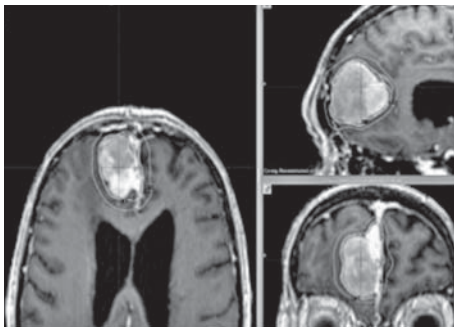

Fig. 4. Parafalcine benign meningioma treated with fractionated stereotactic radiation therapy.

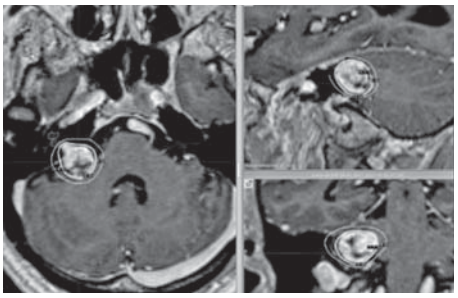

Fig. 5. Acoustic neuroma

and preservation of useful hearing. The technique produces low rates of damage to the fifth and seventh cranial nerves. (Figure 5)

Stereotactic radiation treatments are also used as boost in nasopharyngeal carcinomas with skull base invasion, skin cancer with cranial nerve invasion, base of skull chordoma/chondrosarcoma, arteriovenous malformations and recurrent glioblastoma (GBM).

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Colorectal Cancer Screening

by Izi Obokhare MD, FACS, FCCS, Kate Holder, MS3

In the United States, colorectal cancer (CRC) is the third most common cancer among men and women and ranks second only to lung cancer as a leading cause of cancer mortality. Studies estimate that almost 150,000 Americans will be diagnosed with CRC annually and over 50,000 Americans die annually as a result of this disease (1,2). Colorectal cancer can be an extremely aggressive disease affecting a variety of age groups. Over 7% of anticipated annual deaths will be composed of patients under the age of 50 (1). Recent data collected from 2011 to 2015 estimate that the average incidence of CRC per 100,000 ranges from 45.9 to 34.6 for men and women respectively (2,3). While these numbers are still dismally elevated, they have declined significantly since the implementation of CRC screening (3).

The development of colorectal cancer screening protocols and techniques has remained an ongoing medical concern for almost 100 years. In May of 1927, Lockhard-Mummery and Dukes first demonstrated that CRCs were associated with adenomatous tissue, conceptualizing that CRC does not arise de-novo but progresses from premalignant lesions of the colon via an adenoma-carcinoma sequence (4). This revelation quickly became the central concept behind CRC cancer screening, prevention, and treatment. By the 1930's, staging systems were developed that trended better survival rates in patients who were diagnosed and treated for CRC at earlier stages (4). This research was slow to impact public screening guidelines and was challenged globally until definitively proven in 1993 by the National Polyp Study which confirmed the adenoma-carcinoma sequence (4).

The first screening protocol was implemented at the University of Minnesota in the late 1940's using rigid sigmoidoscopy techniques on asymptomatic patients (4). Even this early study demonstrated a 85% decrease in incidence of CRC among patients who were screened and treated before they became symptomatic when compared to the general population (4). Despite these results, rigid sigmoidoscopy procedures remained unpopular among the general medical community as they were time consuming to perform and uncomfortable for patients. Alternative screening techniques were not developed until the late 1960's (4). The first of these, the guaiac card test, was an in-office screening measure used to detect fecal occult blood (FOB) (4). Patients who tested positive for FOB could then be examined and treated surgically before their CRC progressed. Shortly thereafter, in the 1970's, colonoscopy was introduced into clinical practice, allowing patients with positive fecal occult blood tests (FOBT) to be more accurately diagnosed (4). Additionally, colonoscopy made it feasible to less invasively remove polyps and other premalignant lesions from anywhere along the colon (4). The first randomized control trials concerning CRC screening were conducted in the 1970's using combined screening with FOBT and colonoscopy management. Each trial displayed a reduction in mortality up to 33% among participants, prompting a push for swift implementation of universal screening (4).

By 1997, screening colonoscopy was added to the recommendation guidelines of the American Cancer Society and other medical institutions (4). These guidelines initially recommended that colonoscopy exams be performed at 10-year intervals for all average risk patients. The 10-year interval was based on initial studies which suggested that premalignant lesions could take up to 15 years to transform into CRC. Additionally, resources for screening and physician expertise could not initially meet the demand for more frequent colonoscopy screening guidelines. As CRC screening becomes more widely used, screening guidelines have been updated to optimize successful treatment and prevention of CRC. Currently, the American College of Gastroenterology (ACG) *recommends* CRC screening in

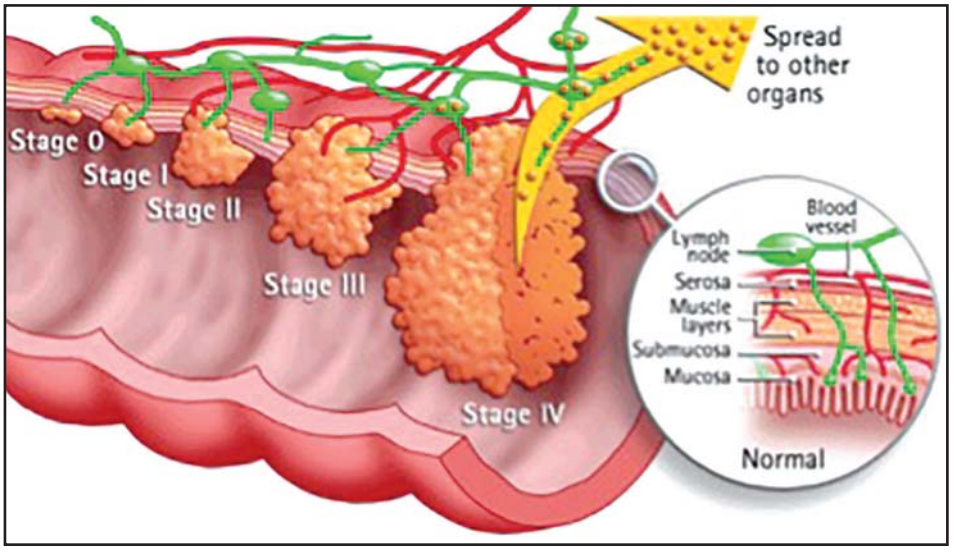

Fig 1. Progression of adenomatous polyps to metastatic colorectal cancer

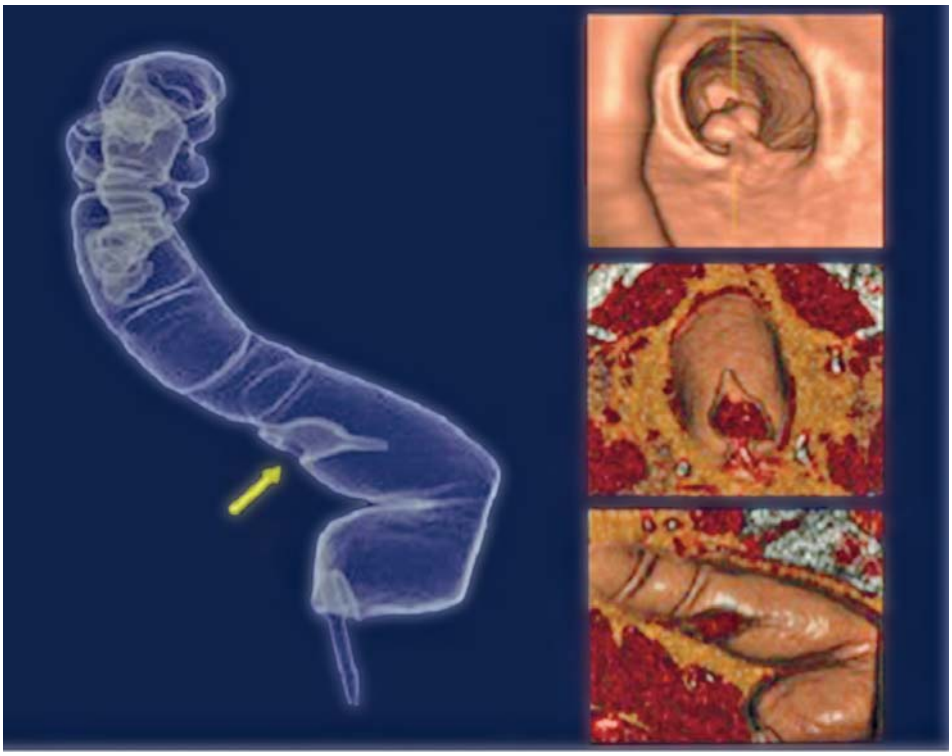

Fig 2. CT colonography

patients age 50-75 and *suggests* CRC screening in patients age 45-49 with an average risk of CRC to reduce incidence of advanced adenoma, CRC, and mortality from CRC. The addition of patients 45-49 to screening protocols was amended in 2021 with the goal of preventing progression of more aggressive cancers in younger patients. Screening beyond the age of 75 should be individualized based on the patient's physiological status.

Biomedical and technological advancements have also broadened screening options for patients' at-home use or physician administration. According to the American College of Gastroenterology (ACG), the ideal screening test should be noninvasive, safe, readily available, convenient, inexpensive, and boast a high sensitivity and specificity (2). While there are many approved screening strategies, the "best" test is one that the patient feels comfortable with and complies with. Screening approaches for CRC can be divided into 1-step and 2-step tests. 1-step tests are also called direct tests and currently include only colonoscopy, which is both diagnostic and therapeutic (2). 2-step tests typically include a less invasive preliminary test followed by a colonoscopy if the initial test is positive (2). Essentially, all tests other than colonoscopy are part of the 2-step test approach. These can include stool occult blood-based tests, flexible sigmoidoscopy, CT colonography, capsule endoscopy or fecal immunochemical tests (FIT). FIT testing has replaced traditional FOBT as it utilizes a more convenient sampling technique, requires no dietary modifications, and has a higher sensitivity for CRC. In the United States, most screenings are achieved with a 1-step opportunistic approach. Currently, ACG recommends colonoscopy and FIT as the primary screening modality for CRC. For patients who are unable or unwilling to undergo colonoscopy or FIT, flexible sigmoidoscopy, multitarget stool DNA testing (Cologard), CT colonography, or colon capsule testing should be performed on an individualized basis.

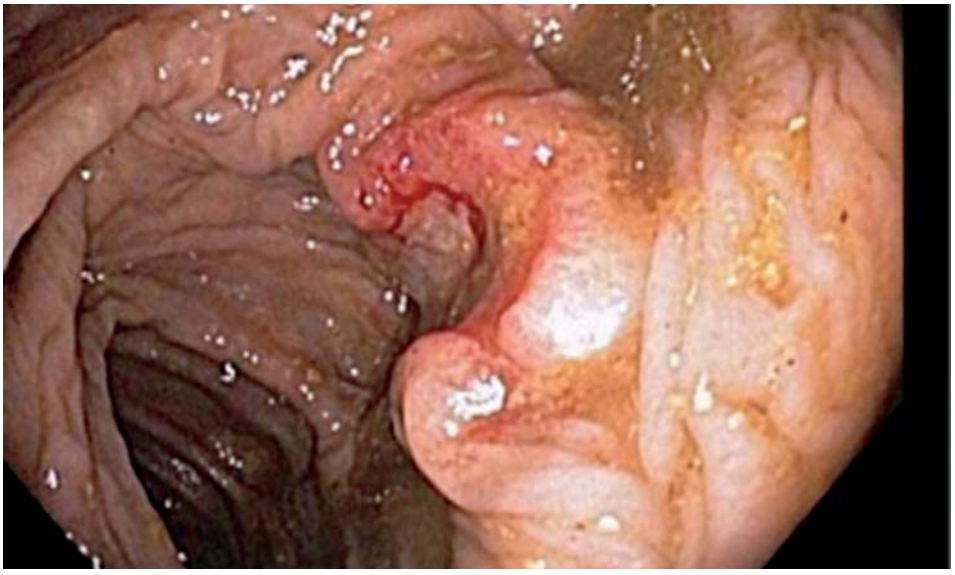

Fig 3. Colonoscopy remains the gold standard for diagnosis.

Since the mid-1980s, when CRC screening was first implemented in some parts of the United States, CRC incidence and mortality have steadily declined by 1.7% and 3.2% respectively each year (2). This decline is thought to be driven by changing risk factors in combination with early detection, removal of precancerous lesions with colonoscopy, and advances in available CRC treatments (2). Unfortunately, despite advances in screening techniques and strong data supporting screening protocols, almost one-third of the eligible US population goes unscreened annually. Rates are even lower in the state of Texas, where only 60% of eligible patients reported up-to-date screening, according to the Texas Cancer Registry (6,7). To increase screening rates, screening tools should be assessed and made more available for varying patient populations based on their willingness to undergo screening and their access to care.

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In the Texas Panhandle, the Cancer Prevention and Research Institute of Texas (CPRIT) has provided grants of over 5.5 million dollars to Texas Tech to aid in the fight against colorectal cancer through the Get FIT to Stay Fit CRC screening program. While serving as the principal investigator, Dr. Obokhare and his team have reached over 1.5 million people via radio, print media, TV, social media, group events and health fairs. Approximately 3000 patients have received screening (75% were being screened for CRC for the first time). 378 colonoscopies have been performed to date and 190 polyps detected and removed. 6 colorectal cancers were diagnosed via the grant. Despite the impact of COVID -19 on CRC screening, the GET FIT to Stay Fit program has developed innovative ways to reach patients through social media and online health fairs. Although colonoscopy remains the gold standard for CRC screening, less expensive options such as the fecal immunochemical stool test (FIT) can be used to screen patient with low or average risk.

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Surgical Aspects of Breast Cancer Care

by Anne Doughtie, MD

Surgical management of non-metastatic breast cancer remains the principal means of eradicating disease, which is then traditionally followed by adjuvant treatments to reduce risk of recurrence. Careful patient selection (while accounting for patient preferences) is crucial to the success and survival of breast cancer patients after surgery. Approximately 1 out of 8 women in the US will develop breast cancer within their lifetime, currently defined to age 80. Some are affected more significantly than others, as clearly each patient's biology is unique, but currently it is estimated that nearly 3.8 million women are living or surviving with breast cancer in the U.S. Most patients are diagnosed over the age of 65 years; however, young people are more likely to present at a higher stage with regional or distant disease. Later stages significantly reduce 5-year overall survival, emphasizing the need for early detection. Breast surgical oncology includes resecting the primary tumor successfully, and then safely employing multi-modality treatments to assist patients with survivorship.

Risk factors and breast cancer prevention

Risk reduction for breast cancer should be aimed at minimizing toxic exposures and reducing levels of estrogen. New studies provide supporting evidence that breast cancer risk can be reduced by enhancing your immune system, specifically with exercise. Lifestyle factors including obesity, poor diet, inactivity, smoking, and drinking alcohol can increase risk of multiple cancers including breast cancer. In particular, stress management is currently being studied as a factor in multiple cancers. A wide literature review reported that moderate exercise (between 20 to 30 minutes daily) leads to a 40% lower risk of death from breast cancer when compared to women who were inactive (9). Increased risks of breast cancer are associated with prolonged estrogen exposures from advancing age, early onset of menses, delayed menopause after age 55, or prolonged use of postmenopausal hormone replacement therapy. Epidemiological studies report that, for every 12 months of breast-feeding, the relative risk of breast cancer is reduced by 4.3% (3). However, delayed childbearing past the age of 30 or nulliparity may increase the risk of breast cancer as well. Extremely dense breast tissue and a family history of breast, ovarian, pancreatic, colon cancer or melanoma are also important factors.

Deleterious genetic mutations can have significant impact on treating breast cancer, as there is an increased rate of secondary cancers among populations with high penetrance such as BRCA1 or BRCA2 genes (7). However, the likelihood of actionable mutations detected on a multigene panel that possibly could change surgical management is relatively low, on the order of 2-5% of all breast cancer patients. Studies are ongoing regarding variants of uncertain significance reported on genetic profiles. Several risk assessment algorithms have been validated (including the Gail model and Tyrer-Cusick scores) that can better help to estimate lifetime risk. Patients with a predicted lifetime risk of greater than 20% should at least undergo annual screening mammography and should be considered for supplemental imaging after discussion with a breast radiologist or breast surgeon.

Imaging: screening and diagnostic

High-quality breast imaging can be classified into two main categories: screening and diagnostic formats. Currently there is no substitute for mammography, either for screening or additional diagnostic studies. Annual routine screening mammography has long been shown to decrease mortality from breast cancer by 20 to 40%, based on multiple population-based studies (4). The 5-year overall survival rate is approximately 99% for most breast cancers if the disease is limited to the breast alone and is detected by mammography. For people of average risk who place a higher value on early detection, annual screening mammography is recommended to begin at the age of 40. When life expectancy is less than 10 years, omission of screening may be considered on an individualized basis. Personalized and dynamic screening that changes with time and integrates an individual's risk factors, genetic studies and predicted lifetime risk is currently being investigated in multiple clinical trials. Screening adjuncts including contrast studies, MRI and ultrasound are best managed by a dedicated breast center.

Beyond screening, appropriate diagnostic studies are used to evaluate clinical symptoms. Symptoms may range from subtle discharge to nipple retraction with itching, scaling or redness or even to skin thickening, swelling and edema, a rare finding that is worrisome for inflammatory breast cancer. Any patient (whether male or female) who presents with a mass within the breast, skin changes of the nipple, chest, or breast, swelling or lymph node enlargement in the axilla or along the clavicle needs further diagnostic evaluation. A red-hot, swollen breast needs an urgent referral to a breast center in order to rule out inflammatory breast cancer. Patients and providers should understand that diagnostic studies often include more than one study dedicated to surgical planning, while disease staging may also require multiple imaging modalities to

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rule out metastatic disease, each serving a distinct purpose.

Breast cancer develops from the glandular tissue, either lobular or more commonly from the ductal components, creating adenocarcinomas with many histologic subtypes. Early noninvasive breast cancer is known as ductal carcinoma in situ or DCIS. If the basement membrane of the epithelial lining demonstrates loss of integrity, then the diagnosis of an invasive breast cancer is made. DCIS is commonly a mammographic finding but can also be associated with vague symptoms. Often DCIS is a more complicated disease from a surgical perspective due to the absence of external clinical signs and microscopic skip lesions. A percutaneous fine needle or core biopsy will diagnose the exact subtype of breast cancer and indicate whether the tumor is sensitive to hormonal treatments or other targeted therapies. Aggressive biologic profiles include HER-2/neu positive disease and breast cancer that does not demonstrate any receptor positivity, known as triple negative breast cancer.

Special circumstances: excisional biopsy

Surgery on the breast can be for benign, high-risk findings or to rule out malignant disease. Current indications for open surgical excisional biopsy include dangerous percutaneous approach or discordant pathology report compared to radiographic findings. Atypical hyperplasia or LCIS may be monitored radiographically for lower risk populations of advanced age or excised to definitively rule out a malignancy. A group of lesions, now described as "high risk", include papillary neoplasm or complex sclerosing lesion, both of which carry increased rates of malignancy on excision; therefore, surgery is often considered. Proliferative fibroepithelial masses are often excised to rule out phyllodes tumor if they have grown, have become symptomatic or are greater than 4 cm of presentation. Other suspicious symptoms such as nipple discharge without abnormality seen on mammography frequently lead to magnetic resonance studies and/or surgical excisional biopsy for both diagnostic and therapeutic purposes. The incidence of upgrade to atypia or carcinoma on final excision should range from 2 to 20% depending on preoperative histology found on core needle biopsy.

Surgical decision-making

Educating patients after diagnosis of breast cancer requires multiple presentations and reiterations on the separate but complementary treatment options. In the age of emerging precision medicine, there is not one single prescription for breast cancer. Personalized therapeutic regimens in conjunction with individual patient priorities improves satisfaction. Multidisciplinary teams include dedicated breast radiology, surgical oncology, medical oncology, radiation oncology, nurse navigators, chemotherapeutic pharmacists and numerous other providers to assist patients with their treatment. Each patient's choice and active participation with expert provider recommendations enriches breast cancer education and enhances decision-making. Similarly, de-escalating care thoughtfully based on evidence in appropriately selected patient groups can be made after thorough multidisciplinary discussion. It is critically

important to seek out experts with additional training specific to breast cancer. Multidisciplinary teams with a special interest in breast cancer are highly skilled in developing precise therapeutic plans for each individual patient.

One of our primary goals in surgical oncology is to plan the best operation at the first operative setting, in order to minimize the incidence of additional second operations. Persistently positive margins or adverse histologic factors may increase the risk of recurrence in the remaining breast tissue. High quality imaging, appropriate employment of preoperative systemic therapy, and risk factor assessment are important considerations prior to surgical intervention. From a surgical standpoint, there is no "more aggressive" surgery, as breast conservation followed by radiation compared to mastectomy produces equivalent disease-free and overall survival outcomes (NSABP B-06). For example, family history and genetic abnormalities are not contraindications to breast conservation, and shared decision making with each individual patient should be performed in conjunction with appropriate genetic counseling and an experienced surgeon. It is important to clearly educate the patient that surgery does not eliminate the possibility of recurrence or metastasis (although surgery combined with adjuvant therapies can reduce these risks significantly).

Historically, surgery for breast cancer was quite morbid, but modern techniques and clinical trials support restoration of a natural appearing breast after either partial or total mastectomy. Breast conserving surgery is a viable and safe surgical option for most breast cancer patients; however, there are certain absolute contraindications. When selecting patients for breast conservation, the extent of disease is a critical factor. The goal of surgical intervention is to completely remove the tumor with negative margins; current margin guidelines are defined as "no tumor on ink" for invasive tumors and 2 mm for carcinoma in situ (6). Large tumor beds (generally considered over 5 cm), extensive or diffuse mammographic abnormalities (such as malignant microcalcifications or architectural distortion associated with the tumor), and multicentric tumors in separate quadrants may preclude partial mastectomy. Tumor to breast volume ratio greater than what can be resected with satisfactory cosmetic results is also contraindication to lumpectomy or partial mastectomy. Again, thoughtful surgical oncologic application of preoperative systemic therapy (i.e., neo-adjuvant therapy) may help to increase the rates of breast conservation.

Surgery on the breast causes a dramatic change in appearance and can be very jarring, creating additional mental trauma in addition to surgical scars. Oncoplastic surgery incorporates traditional surgical oncology techniques with improved cosmetic outcomes. This approach can range from hidden incisions to reduction mammoplasties or more complex reconstruction. Oncoplastic

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surgery techniques can help to preserve native tissue and reduce the incidence of complex multi-stage reconstruction. The greatest benefit may be removing additional tissue with wider surgical margins even in the setting of breast conserving surgery. When performed in conjunction with a plastic surgeon, upper cervical and thoracic pain can be improved with reduction of excessive breast tissue while achieving a more cosmetically appealing and anatomically correct breast position – without compromising the chance to cure the cancer.

Modern perioperative management of the breast surgical patient (including total intravenous anesthesia, enhanced recovery, and long-acting local analgesia) has significantly improved pain control and reduced the use of narcotics and postoperative opioids in the last decade (8). Unfortunately, pain is the most common complication of surgery. Numerous anesthetic techniques have been described in the literature, ranging from epidural anesthesia to paravertebral blocks to novel liposomal suspensions of bupivacaine injected intraoperatively. There is no randomized control trial at this time to determine the safest and most efficacious combination of analgesic techniques. Often, however, an integrated pain regimen can reduce medication use after breast surgery to less than 24-72 hours. Nevertheless, chronic pain and lymphedema can persist for months to years, especially after mastectomy and extensive axillary lymph node dissection.

De-escalation of axillary surgery has long been studied, based on landmark trials from the American College of Surgeons Oncology Group Z-0011 and the After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) group, each of which demonstrated reductions of lymphedema after sentinel lymph node biopsy with similar recurrence rates (1). From these trials, surgeons identified clinicopathologic characteristics including advanced age, higher BMI, increasing number of lymph nodes removed, taxane-based chemotherapy, reconstruction, and comprehensive nodal irradiation, all of which can significantly increase rates of lymphedema. Early intervention (with occupational and physical therapy techniques, as well as manual and mechanical lymphatic decompression therapy) has significantly improved symptomatic lymphedema outcomes within the last several years. Furthermore, careful selection of patients greater than 70 years of age with favorable clinically node-negative, hormonally positive breast cancer may allow de-escalation of axillary node staging (2). Omission of axillary surgery can significantly reduce the risk of lymphedema for this population.

Psychosocial satisfaction varies widely for patients undergoing a partial mastectomy versus mastectomy or additional elective contralateral surgery with or without reconstruction. Multiple studies have demonstrated earlier return to baseline and improved physical wellbeing scores for those patients undergoing breast conservation. However, in patients who have a significant hereditary factor or genetic mutation, choosing bilateral mastectomies has a lower overall decision-regret score. There remains significant psychological trauma after alteration of the breast, even a small resection. In terms of survival, however, contralateral prophylactic mastectomy does not confer additional benefit. This is difficult to communicate to patients with misconceptions of maximizing their surgical intervention. It is challenging to counsel patients with a primary unilateral favorable cancer that additional surgery is not necessary to prevent the current tumor from recurring or metastasizing. The impact of social media influence on surgical therapy cannot be overstated. Over the last two decades, there was a significant increase in mastectomy rate from an estimated less than 5% of all breast cancer surgeries to greater than 25 to 30% of cancer resections after multiple high-profile celebrities were reported undergoing more extensive surgery for hereditary predisposition. Again, we know that the chance of breast cancer recurrence is never eliminated to zero regardless of the surgery selected.

Beyond the operating room: radiation therapy and adjuvant therapy

Radiation therapy remains an important part of almost every breast cancer patient's prescribed regimen to reduce the incidence of local or regional recurrence after surgery, and, in certain cases, to increase overall survival. For example, we know that the 20-year breast cancer specific mortality rate was reduced significantly when patients (especially younger patients) who underwent mastectomy received postmastectomy radiotherapy when they had 1-3 positive nodes on final pathology (5). The NCCN guidelines provide significant evidence to proceed with radiation of the chest wall, supra- and infraclavicular nodal basins, as well as internal mammary chain in patients with more than 4 positive lymph nodes, positive chest wall involvement, T3 tumor greater than 5 cm, or inflammatory breast cancer. If a patient has previously had therapeutic radiation to the chest wall or the ipsilateral affected breast, they may not be a candidate for breast conservation if scheduled to undergo additional radiation. Special considerations for omission of radiation in very select older patient populations should be thoroughly discussed with the radiation oncologist prior to surgical intervention (CALGB 9343). Pregnant women cannot undergo radiotherapy during gestation; therefore, pregnancy is also a relative contraindication to partial mastectomy unless timing of radiation can be delayed until after delivery.

Medical management of breast cancer is incredibly complex due to the natural history and biology of the disease. Most breast tumors are in fact heterogeneous with micro-environments of cancer stem cells, making adjuvant treatments critically important after surgery by utilizing targeted therapy on the cancer cells receptors. Consensus guidelines have been well studied and documented within the National Comprehensive Cancer Network practice strategies for breast cancer. Adjuvant therapies following surgery were previously based on clinicopathologic data and algorithms; however, molecular profiling of breast tumors has led to the emergence of precision-based

medicine. Neoadjuvant chemotherapy regimens are carefully considered in order to reduce tumor burden and preoperatively treat nodal disease. Appropriate patient selection should be discussed among the multidisciplinary team for the most efficacious in-vivo responses prior to resection because each unique biologic tumor profile responds differently.

Breast cancer mortality in the last 20 years has been significantly reduced with improved surgical techniques, modulated radiotherapy, and targeted chemo- and immunotherapeutic agents. Early detection, patient-shared decision making, and expert multidisciplinary cancer management will continue to improve survival as well as patient outcomes in breast surgical oncology.

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Breast Cancer Update

by Srini B. Reddy, MD

In the United States, breast cancer accounts for over 260,000 new cases each year and is responsible for over 40,000 deaths. Breast cancer is the second most common cause of cancer death in women in the US. Breast cancer mortality rates have been decreasing since the 1970s (1). This decrease in mortality is primarily due to improved breast cancer screening and improvements in adjuvant therapy.

Screening

Screening is of greatest value for individuals who are most likely to develop breast cancer and for whom early treatment is more effective than later treatment in reducing mortality. Thus, it is important to determine a person's risk of developing breast cancer and then to use that information to recommend both the modality and frequency of screening. High risk women need to be referred for genetic testing and for consideration of chemoprevention and/or prophylactic surgery.

Screening modalities have improved over the years. Compared with digital mammography, tomosynthesis (3D mammogram) increases rates of cancer detection and decreases recall rates for false-positive mammography readings (2). False-positive means there is an abnormality on imaging that is not due to cancer, which can lead to more anxiety for patients and additional tests and sometimes biopsy to prove that the abnormality is not cancer.

Once a cancer diagnosis is made, treatment involves a multidisciplinary approach, involving surgical oncology, radiation oncology, and medical oncology. This collaborative approach has been associated with a reduction in breast cancer mortality.

Adjuvant therapy

Patients with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy) and regional lymph node sampling or removal of all nodes, with or without radiation therapy. Following definitive local treatment, adjuvant systemic therapy (treatment to eradicate any micro-metastatic disease) may be offered, based on primary tumor characteristics such as tumor size, grade, number of lymph nodes involved and status of estrogen receptor, progesterone receptor and human epidermal growth factor 2 (HER-2 receptor).

Tumor characteristics predict which patients are likely to benefit from which specific type of therapies. For example, hormone receptor positive patients benefit from use of endocrine therapy like tamoxifen or aromatase inhibitors (such as anastrozole). Patients with HER-2 positive cancers benefit from HER-2 directed therapy like trastuzumab with or without pertuzumab.

In patients with *BRCA1/2* mutations and high-risk early HER2-negative breast cancer, adjuvant treatment with olaparib, an inhibitor of poly(ADP-ribose) polymerase (PARP), has been shown to improve disease-free survival outcomes (3).

Most recently, the CDK 4/6 inhibitor, abemaciclib has been shown to reduce risk of breast cancer recurrence in high-risk estrogen receptor positive breast cancer patients when used in combination with estrogen receptor blockers (4).

Another improvement in adjuvant treatment is use of intravenous bisphosphonates (8) in hormone receptor positive, postmenopausal women. Bisphosphonates have been shown to reduce risk of breast cancer recurrence in the bones and to improve mortality.

Neo-adjuvant therapy

Most patients with locally advanced breast cancer, and some with earlier-stage disease (particularly if triple negative and HER-2 positive) are treated with neoadjuvant (treatment before surgery) systemic therapy. The goal of neoadjuvant treatment is to induce a tumor response before surgery and thus, to enable breast conservation. Neoadjuvant chemotherapy also provides information about response to therapy that may be useful in planning further therapy. In the past, we did not know who would benefit from additional therapy to reduce risk of recurrence until recent studies show benefit in patients with residual cancer after neoadjuvant therapy.

Most recently, incorporating immune checkpoint inhibitors like pembrolizumab with carboplatin-containing neoadjuvant chemotherapy for patients with triple negative breast cancer has been shown to improve complete pathological response, which may translate into improved disease-free survival and overall survival (6). Based on this, immunotherapy is approved with chemotherapy for locally advanced triple negative breast cancer patients.

Adjuvant therapy AFTER neo-adjuvant therapy

Patients with hormone receptor-negative, HER2-negative breast cancer (triple negative) who have a complete response to neoadjuvant therapy would typically not receive further chemotherapy in the adjuvant setting, as there is no evidence that the addition of adjuvant chemotherapy improves overall survival. These patients should begin post-treatment surveillance. However, for patients

whose tumor has not had a complete response to neoadjuvant therapy, adjuvant capecitabine may be administered (5). Patients receiving capecitabine had higher rates of five-year disease-free survival and overall survival.

Patients with HER2-positive breast cancer who have a pathologic complete response at the time of surgical resection should complete remaining year of trastuzumab with or without pertuzumab, without the addition of further chemotherapy.

However, in cases where the tumor has not had a complete response to neoadjuvant therapy, adjuvant Ado-trastuzumab emtansine (Kadcyla) (7) for 14 doses rather than trastuzumab with or without pertuzumab is recommended as it is shown to decrease recurrence and improve chances of being alive without cancer.

All the above interventions that have been developed in the past few years have helped reduce the risk of recurrence for all subtypes of early-stage breast cancers.

Management of metastatic breast cancer

Despite improvement in early detection and more effective treatments to prevent recurrence, some patients will recur with metastatic disease and will eventually succumb to the disease. Although metastatic breast cancer is unlikely to be cured, there are meaningful improvements in survival due to availability of more effective systemic therapies. For instance, median survival in patients with metastatic breast cancer (MBC) increased from 21 to 38 months from 1990 to 2010 (17), and patients with estrogen receptor (ER)-positive MBC now have a median overall survival of 57 months (versus 33 months in ER-negative patients).

Although a subset of patients with oligometastatic disease may benefit from an intensified locoregional approach, most patients with metastatic cancer receive systemic medical therapy consisting of chemotherapy, endocrine therapy, biologic therapies, and/or supportive care measures. The primary goals of systemic treatment for metastatic disease are prolongation of survival, alleviation of symptoms, and maintenance or improvement in quality of life. The selection of treatment is tailored individually, taking into consideration the tumor biology and clinical factors.

Several recent improvements in the treatment of metastatic breast cancer are due to discovery of treatments that are targeted to mutations (changes in cancer genes) and newer chemotherapies. Targeted therapies stop tumors from multiplying by targeting and inhibiting specific receptors that promote tumor growth (for details, see the article by Dr. Leonardo Forero in this issue).

For estrogen receptor positive tumors, several new treatment options successfully employ CDK 4/6 inhibitors (palbociclib, ribociclib and abemaciclib), PI 3 kinase inhibitors (alpelisib) or mTOR inhibitors (everolimus), in combination with estrogen receptor blockers to improve and prolong response, thereby, extending lifespan of breast cancer patients (9,10,11).

We also have new treatments available for HER-2 positive breast cancer patients, in addition to trastuzumab and pertuzumab based treatments. There are new antibody-drug conjugate therapies like Ado-trastuzumab emtansine (commonly known as Kadcyla), fam-trastuzumab deruxtecan (Enhertu), oral tyrosine kinase inhibitors like tucatinib, Neratinib and a Fc-engineered anti-HER-2 receptor monoclonal antibody called margetuximab, which are used by themselves or with combination of chemotherapy, shown to improve response and prolong life (12,13,14).

New treatments are also available in the most difficult to treat subgroup of triple negative breast cancer. Those

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who have germline mutation in BRCA1 and 2 would benefit from PARP inhibitors like olaparib and those who have specific tumor characteristics like high tumor mutation burden and PD L1 expression would benefit from immune checkpoint inhibitors like pembrolizumab (15). There is also antibody drug conjugate therapy, Sacituzumab govitecan (Trodelvy) that is shown to be very effective in controlling disease in triple negative breast cancers (16).

Despite advances in screening and therapies as detailed above, some patients still succumb to disease. Several alternative strategies are under investigation incorporating newer targeted therapies and immunotherapy for early-stage cancers to prevent recurrence and develop metastatic disease, thereby, improving chances for cure. Similarly, new strategies and combination therapies are being studied to improve long-term survival in patients who do develop metastatic disease.

Summary

We all should strive to identify high risk patients, modify risk factors and offer preventive therapies to reduce breast cancer incidence. Patients should be encouraged to get appropriate cancer screening to detect cancer early when it is curable. Several advances in adjuvant and neoadjuvant therapies as described above have significantly reduced the risk of recurrence. Finally, those who develop metastatic disease despite above therapies live longer (sometimes several years longer) with advances in the treatment of metastatic disease.

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Chemotherapy: A Historical Review

by Rouzbeh K Kordestani, MD, MPH

Chemotherapy has been integral to the treatment of many cancers over the past 80 years. It would be difficult to calculate the number of lives saved and/or prolonged by the use of modern antineoplastic drugs. Chemotherapy – now supplemented by immunotherapy and targeted chemicals – has been the foundation of cancer treatments in most of the cancer centers in the modern world. That being noted, it is hard to imagine that chemotherapy arose from deadly gases such as mustard gas that were initially used in the chemical warfare arenas of Europe during World War I.

The Great War

No wars are great. However, in light of the little knowledge or prescience known in the early 20th century, World War I was referred to by many as "the Great War." The war was fought mostly in Europe and Asia and was thought to be the first war of global extent ever to plague humankind. As the war dragged on and continued to extract a heavy toll on the countries of Europe, it became a war of attrition. The warring factions simply held their lines of conflict and made little progress against one another. In an attempt to break the stalemate, chemical warfare was begun. It is hard to know who to blame. Soon, however, all the European powers as well as the United States were using deadly gases such as mustard gas in the arenas of war.

The Hague Conventions of 1899 and 1907 specifically forbade the use of chemical weapons. However, as in all wars, things did not exactly go according to plan. As early as April of 1915, German troops released chlorine gas into the fray against their French, Moroccan, and Algerian adversaries in the Battle of Ypres. In the next series of battles, this misadventure became an accepted modality of warfare and was used by both sides. Soon, chlorine gas was replaced by mustard gas which seemed to be more effective and deadly. Mustard gas became the standard and was used regularly until the end of the conflict. By war's end, estimates placed the number of troops exposed to mustard gas at close to 1.5 million, with almost ninety thousand fatalities.

As the war slowly ground to a halt, the participants agreed that no such weapons should again be used against humankind. An agreement was made in Geneva in 1925 (the Geneva Gas Protocols) that no country or power should ever again resort to the use of chemical weapons in the arena of warfare. Interestingly, though, with the use of mustard gas now forbidden, the fascination with the data obtained during "The Great War" only began to grow. Reports of autopsies noted that, in the corpses of many troops exposed to the mustard agents, severe lymphoid depletion, bone marrow changes and neutropenia were present. In addition, medical experts and scientists noted that mustard gas seemed to have an effect on cancer tissues, and actually caused a slowing effect. Unfortunately, since the chemicals were restricted, little additional information was forthcoming, and there was no data by which to understand an actual cause-and-effect relationship. The data simply did not exist to further this hypothesis. That changed with World War II

The Second World War and the SS John Harvey

As World War II began, members of the Allied forces were suspicious of the intentions of the Axis forces. No side wished to violate the international rules or the Geneva Protocols of 1925, but no side wished to be poorly equipped in case the other resorted to its last options. For this reason, both sides secretly continued to produce and stockpile chemical weapons.

By late 1943, the Allied forces had driven the Germans from North Africa and Sicily. While Allied ships were gathered in the Italian port of Bari awaiting unloading, they were attacked by German bombers. One of the ships there that was struck was the SS John Harvey. It was secretly carrying a cargo of 100 tons of liquid mustard gas, along with millions of gallons of gasoline. When it was struck, the explosion that ensued caused thousands of allied troops to be exposed to the mustard gas. The reports of deaths and chemical exposure were quickly suppressed by the Allied general staff so as to not show a violation of international law. Churchill and Eisenhower both denied any such event. Churchill even ordered the mustard gas exposures to be recorded as combat-related dermatitis.

Lt. Colonel Steward Francis Alexander was a chemical warfare expert and an American physician tasked with the study of patients from the SS John Harvey incident. From the autopsies, he quickly noted the presence of the mustard gas and its effects. Similar to the findings in World War I, Dr. Alexander noted bone marrow suppression and lymphoid tissue changes. From this, he noted that mustard gas had arrested the division of certain types of rapidly-growing cells, specifically cancers. Dr. Alexander then theorized that the use of mustard gas may be helpful in suppression of cancer cell growth.

| *continued on page 44*

Goodman and Gilman and the Post-War Efforts

Although incomplete as to cause and effect, Dr. Alexander's findings were significant enough to spur interest in the possible benefits of the use of chemicals in cancer. Two pharmacologists from Yale University, Dr. Louis Goodman and Dr. Alfred Gilman, were contracted by the United States Department of War to further this area of study. As Drs. Goodman and Gilman quickly realized, mustard gas was too dangerous to be used in a lab setting. Because of this, they chemically exchanged a nitrogen molecule for a sulfur molecule, creating a more stable compound – nitrogen mustard. They then began to experiment with nitrogen mustard on lymphoid tissues and lymphoma. In mice induced to develop lymphoma, they showed initial success and remission of the cancer cells. They then recruited the help of a thoracic surgeon, Dr. Gustaf Lindskog, to inject a human patient suffering from non-Hodgkin's lymphoma with a derivative of the nitrogen mustard. They showed that the patient lived much longer (96 days) than expected and that lymphomatous cells were suppressed. Unfortunately, this was only a very limited amount of information from which to extrapolate. Their success did, however, pave the way for the belief that chemicals such as nitrogen mustard could be used in the arena of cancer care. Due to the war effort and the stigma associated with using chemical weapon- based technologies, the data related to Drs. Goodman and Gilman's work and that of Dr. Lindskog were not published until after the war, in 1946. In the meantime, the preliminary data spurred many government scientists in the later years of the war to begin work on other avenues of chemical treatment for cancers.

Farber and Lady Lasker: Science and Politics

Shortly after the Second World War, Dr. Sidney Farber, a pathologist at Harvard Medical School, began to experiment with the use of folic acid and folate analogues. He based his findings on the work of British hematologist Dr. Lucy Wills. Years earlier (1937), working in India, Dr. Wills had shown that, in children with acute lymphoblastic leukemia (ALL), folic acid and/or folate derivatives could increase the size of their tumors. Dr. Farber reasoned that folate was somehow essential to this type of cancer growth and wondered if folate antagonists might help suppress cell growth in children with ALL. His initial work with these chemicals did in fact prove just that. The first such analogue, amethopterin (now known as methotrexate), induced remission in some children, thus bolstering Dr. Farber's theory.

Dr. Farber continued his work at Harvard and was soon championed by Mrs. Mary Woodward Lasker. Mrs. Lasker was herself not a physician, but she was politically savvy and quite wealthy. She decided to support Dr. Farber's work and soon used her political influence to take control of the American Society for the Control of Cancer (She helped to change the name to the American Cancer Society). She then pushed for additional funding from Congress for the organization. By 1948, the funding had grown to $14 million (from an initial budget of $100,000). Over the next few years, Mrs. Lasker redoubled her efforts and was able to get congress to fund the development of the Cancer Chemotherapy National Service Center (CCNSC) in 1955. Her efforts, along with those of Dr. Farber at Harvard, helped boost the budget at the National Institutes of Health from $2 million (in 1946) to $460 million in 1961.

Mary Lasker continued her work until her death. She and her husband were responsible for the development of the prestigious Lasker Prize, highlighting biomedical advances. Even though she was criticized over the years for fostering "Mary Lasker's war" on cancer, her contributions to the landscape of cancer care and the development of chemotherapy were undeniable.

The Birth of Combination Therapies

The advent of nitrogen mustard and folate analogues such as methotrexate showed promise in cancer care. However, significant stigma still accompanied use of chemotherapeutic drugs. As late as the late 1950s, there still was no recognized field of medical oncology. Many physicians, unfamiliar with the data, considered the use of such drugs as "poisons." Within this context, it remained difficult to advocate for effective chemotherapies.

As data began to accumulate, it became obvious that the use of single agents for therapeutic cures was not as effective as the use of combination therapies. Very few single agents were "silver bullets", treating one cancer effectively. Instead, as data was compiled by the 1960s, it became obvious that most effective treatments depended on combinations of chemicals, such as VAMP (vincristine/amethopterin (methotrexate)/6-mercaptopurine/prednisone) for childhood ALL and MOPP (nitrogen mustard/Oncovin (vincristine)/procarbazine/prednisone for Hodgkin disease. The use of combination therapies

increased the rates of remission up to 60% in some cancers. In others, combination therapies effectively "cured" patients, without any relapse.

Years later, this modality of treatment (combination therapy) was effectively proven by Drs. Goldie and Coldman. They developed a model of tumor cell growth in which cell mutations arise at a constant rate. With this thought in mind, clones of cancer cells could develop resistance to certain therapeutic agents. With the use of combination therapies (with different mechanisms of action), however, even resistant cell populations could be exposed to chemicals to which they were sensitive. In this manner, all resistant cell populations could be controlled and sometimes eradicated.

The Age of Targeted Therapies and Monoclonal Antibodies

As more data was compiled from cancer patients, it became apparent that signaling pathways were essential to the function of cells. More importantly, research on signaling pathways showed that, in cancer cells, many of these signaling pathways were altered, at times radically, leading to the abnormal growth patterns seen in highly proliferative tumors. Because of advances in this area, the National Cancer Institute (NCI) began investing heavily in the area of molecular biology in the 1980s.

By the mid-90s, advances in biology and signaling pathways had led to the discovery of the first tyrosine kinase inhibitor (imatinib mesylate). Imatinib was used as a binding protein causing an effective block of an abnormal signal in patients with chronic myelogenous leukemia. This agent, and others like it, highlighted the fact that many abnormalities in cancer cells and cancer cell growth were due to signaling errors or abnormalities in protein kinases.

Around the same time as the development of protein kinase inhibitors (in the 1990's), monoclonal antibodies emerged as targeted therapies in cancer care. MoAbs or monoclonal antibodies were found to be effective chemotherapeutic agents, useful in combination with other agents to target cancer cell receptors. Rituximab is an example of such a monoclonal antibody, designed specifically to block B-cell proliferation in non-Hodgkins lymphoma patients.

The Future

Chemotherapy as a specialty was born in war. It is hard to imagine that chemicals once used to kill thousands can now be used safely and effectively to save the lives of children and adults. The conversion of these deadly chemicals into life-saving cures is a true testament to the ability of science and scientists to look beyond the horizon. Modern chemotherapy has grown to be a formidable part of medicine and science. It may have started with nitrogen mustard, but it has now grown into thousands of chemicals, combination therapies, single agent therapies, adjuvant therapies, and targeted therapies.

As the world becomes more digitized, it is likely that medical knowledge and care becomes more mainstream. Within this new arena, it is hoped that artificial intelligence can be used to help better design chemotherapy drugs that can use targeted modalities and genetic information to save even more lives. Chemotherapy may have had humble beginnings, but its future is truly bright.

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Rise and Shine: *Advancement in Sunscreens and Practical Application*

by Kate Holder, MS3

Since almost the beginning of recorded history, humans have been interested in manipulating the sun's effect on skin. In ancient Egypt, a concoction of rice bran, jasmine, and lupine was used to prevent tanning while ancient Greeks preferred olive oil (1). The first modern 'sunscreen' was commercially produced in the 1920s after the UV wavelengths responsible for sun damage were described by Vahle (2). By the 1930s companies like L'Oréal were mass producing benzyl salicylates as sun protectants, and by late 1970, the US Food and Drug Administration (FDA) began regulating these products as drugs (3). Today, an array of liquid, gel, and powder formulas are available to prevent sun damage.

In recent decades, consistent use of sunscreen has been proven to prevent photocarcinogenesis and delay development of detectable photoaging (4,5). Some studies suggest that daily use of SPF may visibly reverse the signs of pre-existing photodamage, including surface texture and skin tone, by protecting the skin and allowing it to rejuvenate while also preventing new sun damage (6). Additionally, regular use of sunscreen has proven to be efficacious at preventing a variety of skin cancers, including melanoma (7). Despite the variety, availability, and proven efficacy of sunscreen, only 1 in 10 Americans use sunscreen regularly, and close to 60% of Americans report no regular sunscreen use at all (8). This may explain why, despite advancements in sun protection, incidence rates of cutaneous melanoma and keratinocyte skin cancers including squamous cell carcinoma and basal cell carcinoma are rising (9). The American Cancer Society projects that almost 100,000 new melanomas will be diagnosed in 2022, and an estimated 7,650 Americans will die of melanoma within the year (10). In Texas, the rates of cutaneous malignancy are even higher, with one in three Texans developing skin cancer within their lifetime (11).

In addition to proper education concerning sun exposure, helping patients choose a sunscreen that fits their needs may encourage regular application and decrease instances of sun damage. Today, most commercially available sunscreens fall into two categories based on their mechanism of action: chemical and mineral. Some formulas contain both chemical and mineral protectants mixed at varying ratios. Efficacy of mineral and chemical sunscreens is graded using sun protective factor (SPF), a numerical value denoting the degree of ultraviolet light protection. While even low SPF products are efficacious, the American Academy of Dermatology recommends regular use of sunscreen with SPF of 30 or higher.

Chemical sunscreens, also called organic sunscreens, absorb UV light and traditionally provide superior aesthetics upon application (12). These usually contain octisalate and avobenzone (12). In recent years, chemical sunscreens have been shown to have some systemic absorption, which is not necessarily harmful but has been a source of much controversy (12). Additionally, chemical sunscreens are often not tolerated by patients with allergic tendencies.

Mineral sunscreens, also known as inorganic or non-carbon based sunscreens, work by scattering UV light rather than absorbing it (12). These formulas, which often contain titanium dioxide and zinc oxide, have less or no systemic absorption, protect against additional blue light, and have decreased potential for allergic sensitization (12). For patients with sensitive skin, mineral sunscreens may provide the best protection with the least discomfort. However, the reflective properties of mineral sunscreens have traditionally caused unwanted shine and white sheen upon application, limiting their cosmetic satisfaction.

New tinted mineral formulas may mitigate the cosmetic disadvantages of mineral sunscreens without sacrificing their familiar, gentle formula. Additionally, the 'tint' in these formulas allows them to provide true broad-based coverage against both ultraviolet and visible light. This added protection against visible light can prevent dyspigmentation – specifically, erythema – in light-skinned patients and pigmentation in dark-skinned patients. Overall, tinted mineral sunscreens may combine the most favorable cosmetic outcomes with the widest coverage against ultraviolet radiation and visible light, protecting against aging and free radical damage.

Healthcare providers should regularly counsel patients on appropriate use and application of sunscreens. Patients should be encouraged to try new tinted mineral formulas if they have had difficulty finding a suitable product in the past. While the formula, SPF, and spectrum of light coverage can be adjusted to fit individual patient needs, the consistent and correct application is required for both cosmetic and anti-photocarcinogenic results. Modern sunscreens may take a different appearance than the oils of ancient Egypt and Greece, but ongoing efforts are still needed to educate patients about the benefits of sunscreen and the morbidity and mortality associated with light radiation.

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B-cell Acute Lymphoblastic Leukemia Mimicking a Malignant Bone Tumor in a 5-year-old Male

by Chukwunonye Ogbuji, MD (PGY-1); Niki Sankoorikkal, (MS3); Alexis Schuck, (MS3); Samer Zaid-Kaylani, MD; Smita Bhaskaran, MD

Introduction

Leukemias arise due to clonal expansion and arrest of normal precursor white blood cells at a specific stage during proliferation. Acute lymphoblastic leukemia (ALL) is the most common childhood leukemia, and the B-cell subtype (B-ALL) primarily affects the B-lymphocytes. The overall incidence of pediatric ALL during 2001-2014 was 34.0 cases per 1 million persons and among all racial/ethnic groups was highest among Hispanics (42.9 per 1 million) (1). Peak incidence is between 2-5 years. Ionizing radiation, chemicals, drugs, and chromosomal abnormalities are some of the most frequently implicated factors in the pathogenesis of ALL. ALL can present with bleeding, fever, enlargement of lymph nodes, liver, and spleen, as well as bone pain. In 25% of cases, bone pain is the first symptom. Bone pain results from direct leukemic infiltration of the periosteum, bone infarction, or expansion of the marrow cavity by leukemic cells (2).

Case Presentation

A 5-year-old male was referred to the Texas Tech pediatric hematology and oncology clinic for evaluation of severe pain and swelling in the left shin following a fall at school. He woke up at nights crying because of the pain and had developed a limping gait. He had no history of fever, weight loss, drenching night sweats, or difficulty breathing. Physical examination revealed a bony swelling around the proximal left tibia. An initial x-ray showed an ill-defined focus of moth-eaten appearance in the proximal left tibia, with soft tissue swelling, suggestive of an infiltrative process. Magnetic resonance imaging confirmed an aggressive bone lesion in the proximal left tibial metaphysis along with periosteal elevation. Nuclear bone imaging showed a focal abnormality within the proximal left tibia, also suggestive of a primary bone tumor with no evidence of metastatic disease. Complete blood count was normal with normal white blood cell, red blood cell and platelets. There was no evidence of tumor lysis. No dysplastic cells or blasts were noted on a peripheral blood smear. The bone tumor was initially suspected to be Ewing sarcoma. These findings prompted biopsy of the left tibial lesion. Pathological examination showed a monomorphic population of lymphoid cells. Further investigations, including a bone marrow aspiration and biopsy, demonstrated 60% and 24% lymphoblasts in the right and left iliac crests respectively. These findings confirmed the diagnosis of B-ALL. The patient was treated per the standard of care, following the Children's Oncology Group protocol. The patient is currently in remission and has reported no further episodes of bone pain.

Discussion

The most common pediatric cancers are hematologic malignancies (ALL, Hodgkin lymphoma, Non-Hodgkin lymphoma), solid tumors (Ewing sarcoma, osteosarcoma, Wilms tumor, rhabdomyosarcoma), and CNS tumors. ALL is the most common cancer diagnosed in children, contributing to 25% of pediatric cancer diagnoses. It is further divided into B-ALL and T-ALL immunophenotypes. While it commonly presents in sites of lymphocyte development (especially bone marrow), extramedullary manifestation can occur. Risk factors include radiation exposure, infection with HTLV-1 or EBV, and genetic syndromes (Down syndrome, Fanconi anemia, Li Fraumeni syndrome, etc.). Prognosis in pediatric patients is good with > 95% achieving complete remission after induction chemotherapy (3).

Treatment for ALL is coordinated at cancer centers via a multidisciplinary approach, consisting of pediatric oncologists, subspecialists, social workers, child-life specialists, and psychologists. Treatment intensity and prognosis are dependent on pre-treatment risk factors including immunophenotype, presence of extramedullary disease, steroid pretreatment, presence of Down Syndrome, and National Cancer Institute (NCI) risk group classification. ALL therapy consists of remission induction chemotherapy at the time of diagnosis, followed by postinduction therapy, consisting of consolidation/intensification and maintenance (3). Patients who fail to achieve first complete remission become candidates for allogeneic hematopoietic stem cell transplantation (HSCT).

Refractory ALL cases have typically been treated with HSCT. Outcomes have improved over the years, as HLA matching has decreased the incidence of graft-versus-host disease and additional treatments preventing relapse. These supplemental treatments include donor lymphocyte infusion, targeted immunotherapies (monoclonal antibodies and natural killer cell therapy) and the withdrawal of immunosuppression. Chemotherapy refractory B-ALL patients who have received HSCT have done well with chimeric antigen receptor (CAR) T-cell therapy. This therapy uses engineered T-cells with chimeric antigen receptors to redirect T-cells to target malignant B-cells affected in B-ALL and has been proven to be useful in refractory cases of ALL. New treatment agents and regimens are constantly under development through clinical trials and organizations like the Children's Oncology Group (4).

The Children's Oncology Group (COG) and pediatric cancer care

The Children's Oncology Group (COG) is an international research organization primarily supported by the National

Cancer Institute (NCI). This group originated from the cooperative group system for clinical research, which began in 1955. At the end of the 1990s, four cooperative groups based in North America, the Children's Cancer Group (CCG), the Pediatric Oncology Group (POG), the Intergroup Rhabdomyosarcoma Study Group (IRSG), and the National Wilms' Tumor Study Group (NWTS), combined to form the Children's Oncology Group. This merger consolidated the resources of the individual groups and has, in the opinion of many, contributed to a substantial improvement in survival rates for childhood cancer (3). ALL in particular has evolved from a virtually incurable disease 50 years ago to one with a 5-year survival rate approaching 90% (5).

The spectrum of COG research ranges from common forms of childhood cancer, such as ALL, to very rare childhood cancers, such as retinoblastoma and hepatoblastoma (4). Along with disease- specific research endeavors, the COG conducts studies in developmental therapeutics (including stem cell transplantation), epidemiology, supportive care, and behavioral sciences and survivorship (4). The COG now has more than 10,000 scientists worldwide working together to improve the outcome for children with cancer. The COG continues to expand their research efforts with nearly 100 clinical-translational trials active at any given time. In the United States, 90-95% of all individuals under age 15 with a newly diagnosed malignancy are cared for at a COG institution. Furthermore, 50-60% of children are enrolled in clinical trials. Continuing trials and research allow opportunities for advancement in treatment, consolidation of resources, and coordinated care and support for patients and their families. We are proud that Texas Tech and Northwest Texas Hospital have been part of the COG effort in Amarillo and the panhandle since 1995.

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