Women’s Cancer

PATRICK I. BORGEN, MD, on

The Evolution of Breast Cancer Care

‘Looking for a kinder, gentler way to treat the disease’

GI Cancer Patient-Reported Outcomes Show Quality of Life Improvements for Newer Drug Combinations

Kevin Wright

Lung Cancer Synchronous Bilateral Lung Cancer

Mehmet Sitki Copur, MD, FACP; Rudy Lackner, MD, FRCP; Whitney Wedel, MD; Nikki Lintel, MD; Mathew Stritt, MD; and Kalpesh Ganatra, MD

Hematologic Malignancies Isolated Extramedullary Relapse in Acute Lymphoblastic Leukemia

Santiago Riviello-Goya, MD; Aldo A. Acosta-Medina, MD; Sergio I. Inclan-Alarcon, MD; Sofía Garcia-Miranda, MD; Christianne Bourlon, MD, MSc

Immunotherapy A 79-year Old Man with Itchy Erythematous Patches

Mehmet Sitki Copur, MD, FACP; Susan Corey, MD

GU Cancer FDA Approves Pembrolizumab for BCG-Unresponsive NMIBC

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Advancing the Field of Breast Cancer Care

Dear Reader,

With the treatment landscape for breast cancer continuing to evolve, survival rates are increasing, and patients are doing better now than they have ever done before. But with evolving therapies comes complex decisions, and meetings like the 37th Annual Miami Breast Cancer Conference help to bring healthcare providers in this space together to parse out the data behind those decisions.

In this issue of ONCOLOGY, we spoke with Patrick I. Borgen, MD, chair of surgery and director of the Breast Cancer Program at Maimonides Medical Center and the meeting's program chair, on the current state of the field, and the evolution of treatment that he has witnessed and been a part of during his storied career. “I was there for [the] transition from mastectomy to lumpectomy, from mastectomy to breast conservation therapy,” Borgen says. “We played a significant role in the design, development, and popularization of sentinel node biopsy. The development of nipple-sparing mastectomy was reconstruction, [and] we were there at the very beginning of that.”

Borgen also discusses the need for a multidisciplinary approach to treatment, the lessening role of surgical treatment, and the rise of immunotherapy and targeted agents. “I think no one who really thought this through [years ago] felt that the future of prophylaxis would be radical surgery,” Borgen notes. “And so, the answer had to be medical, it had to be genetic, it had to be genomic.”

Also in this issue, you will read of 2 patient scenarios: A 43-year-old male with past history of B-cell acute lymphoblastic leukemia, and a 70-year-old woman with newly diagnosed synchronous multiple primary lung cancer. How do we treat them? Our expert contributors go in depth on best practices and optimal treatments.

Within these pages, you will also find highlights from the 2020 Gastrointestinal Cancers Symposium, and a breakdown of the FDA’s recent approval of pembrolizumab (Keytruda) for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ.

I hope you find our journal helpful in caring for your patients through what is likely one of the most challenging times in their lives. As always, thank you for reading.

- Mike Hennessy, Sr.
Chairman and Founder of ONC’s parent company, MJH Life Sciences

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Isolated Extramedullary Relapse in Acute Lymphoblastic Leukemia: What Can We Do Before and After Transplant?

Santiago Riviello-Goya, MD1; Aldo A. Acosta-Medina, MD2; Sergio I. Inclan-Alarcon, MD3; Sofia Garcia-Miranda, MD2; and Christianne Bourlon, MD, MHSc2

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A 43-year-old male with a history of B-cell acute lymphoblastic leukemia (ALL), who underwent allogeneic hematopoietic stem cell transplantation (HSCT) 5 months prior, presented to the emergency department with a 5-day history of progressive bilateral lower extremity weakness. On physical examination, there were no additional neurologic findings; sensory function and urethral and anal sphincter tone were preserved.

Initial clinical laboratory testing showed peripheral blood cell counts, a peripheral blood smear, and a comprehensive metabolic panel within normal limits. Neuroimaging by computed tomography (CT) and magnetic resonance showed no evidence of acute intracranial processes or lesions suggestive of leukemic relapse. A lumbar puncture for cerebrospinal fluid (CSF) analysis was performed, and documented the presence of lymphoid-appearing blasts.

Figure 1 Light microscopy of Wright-stained CSF showing uncountable lymphoid-appearing blasts.

Is the risk of iEMR following HSCT modified by the choice of conditioning regimen? If so, which of the following approaches would have been the best choice to prevent iEMR in this patient?

A. There is no role of conditioning therapy in preventing iEMR
B. Reduced intensity of regimen to favor graft-versus-leukemia (GVL) effect
C. Nonmieloablative regimens including fludarabine
D. Mieloablative regimens including total body irradiation (TBI)

TURN TO PAGE 40 for the answer and a discussion of this case by experts.
blasts (Figure 1). Flow cytometry (FC) confirmed central nervous system (CNS) infiltration by B-lineage lymphoid blasts (CD34+, CD45+, CD22+, CD19+, and CD10+) (Figure 2). Bone marrow aspirate and biopsy, including FC evaluation, were negative for systemic relapse. Bone marrow chimerism was 98%.

With a diagnosis of isolated extra-medullary leukemic relapse (iEMR), the patient was initiated on weekly intrathecal chemotherapy and was weaned off graft-versus-host disease (GVHD) prophylaxis, achieving CSF clearance after 4 weeks of therapy. Against Hematology service recommendations, the patient declined systemic therapy and received only whole brain radiation therapy (24 Gy in 12 fractions). The patient experienced remission of neurologic symptoms; however, after 5 months, he developed bilateral testicular tenderness and enlargement.

An ultrasound was performed and was suggestive of leukemic infiltration (Figure 3). Chemotherapy with methotrexate and L-asparaginase in addition to radiotherapy to the testes (24 Gy in 12 fractions) was given without complications.

One year after initial CNS iEMR, the patient developed overt bone marrow relapse (BMR), as evidenced by development of bone pain throughout the lumbosacral region, and the appearance of multiple blastic and lytic lesions throughout the appendicular and axial skeleton. A positron emission tomography-CT scan documented abdominal lymphadenopathy (Figure 4). With this rapidly progressive picture, the patient was transitioned to supportive care and died 2 months later.

Discussion
Allogeneic HSCT is an effective treatment for ALL, which can achieve long-term remission and even a potential cure.1 Antineoplastic activity is dependent on both high-dose chemotherapy and graft alloreactivity, with the latter manifested in the GVL effect, and undesirably yet inherently, in GVHD.2 Despite recent advances in allogeneic HSCT strategies, disease relapse is common and remains the most important cause of death in this population. Relapse is reported in 30% to 40% of patients, but can increase to 60% in patients who are in a second complete remission (CR) at time of HSCT.2,3

Risk factors for relapse in patients with ALL who have undergone HSCT include disease- and transplant-related features. Reported high-risk disease characteristics include: hyperleukocytosis at diagnosis (white blood cell count >30 x10⁹/L for B-lineage ALL and >100 x10⁹/L for T-lineage ALL); cytogenetics associated with poor outcomes, including chromosome 11 translocations and t(9;22); a short remission timespan; more than a first CR; and a failed or delayed

**Figure 2** Flow cytometry of CSF showing a CD34+, CD45+, CD19+, CD22+, and CD10+ population (blue) consistent with CNS infiltration by B-lineage acute leukemia.
remission after induction therapy. In the HSCT population, transplant-related factors should be considered, including alternative donors other than those who are matched related and matched unrelated, the type of conditioning regimen, and the development of GVHD.

ALL relapse following HSCT most commonly involves the medullary compartment, with a cumulative incidence of 41% at 5 years. Conversely, extramedullary relapse (EMR) is uncommon, with a 5-year cumulative incidence of 11.0% and 5.8% for EMR and iEMR, respectively. Due to the rarity of EMR, its prognostic impact remains controversial and the ideal management strategies are a subject of active study.

EMR is associated with poor clinical outcomes; however, the subgroup of patients with iEMR (as presented in this patient case) is gaining attention due to its increasing frequency, its role heralding a systemic relapse, and its clinical behavior showing better survival outcomes compared with BMR and EMR.

Isolated EMR is defined as the presence of clonal blasts in any tissue other than the medullary compartment; bone marrow evaluation must show less than 5% of clonal blasts and a full donor chimerism. Most commonly affected sites include the skin, soft tissues, lymph nodes, and immune sanctuaries including the CNS and testes. Because prevention rather than treatment of relapse is related to improved survival outcomes, it is important to define subgroups of patients who may benefit from early intervention with a personalized transplant strategy.

Higher rates of iEMR have been linked to patients of younger age. This is thought to be secondary to: (1) a higher incidence of ALL compared with acute myeloid leukemia (AML) in this age subgroup, the former of which is most associated with EMR; (2) the relative overrepresentation of myelomonocytic/monocytic phenotypes in AML presenting in young individuals; and (3) the higher likelihood of a history of EMR in children compared with adults.

A history of extramedullary (EM) disease, which has consistently been found to impact the development of iEMR, is preexistent in up to half of patients. In 2 out of 3 cases of EMR, disease affects the site of original EM involvement, possibly due to low efficacy of both high-dose chemotherapy and the GVL effect. An exception to this is CNS involvement, despite being a risk factor for subsequent CNS iEMR, which is commonly reported de novo, reflecting the protective effect of regularly administered prophylaxis to patients at high risk of CNS infiltration.

The effect of GVHD on risk of iEMR is highly nuanced. Despite its well-known role as a protective factor for BMR, the same effect does not appear to hold true for iEMR. Initial reports in this population showed no differences in relapse-free survival regardless of acute or chronic GVHD (cGVHD) or a positive association between extensive cGVHD.

Figure 3 Ultrasound of the testes showing diffuse bilateral hypoechogenicity and increased vascularity, suggestive of leukemic infiltration.
and iEMR development.\textsuperscript{10,13} This has led to investigators to postulate that the underlying physiopathology differs among different types of relapse, with decreased expression of human leukocyte antigen (HLA) minor histocompatibility antigens and adhesion molecules and decreased penetration of both immune cells and high-dose chemotherapy to EM sites.\textsuperscript{14} These mechanisms lead to decreased effectiveness of T-cell dependent cytotoxicity of donor lymphocytes as compared with the medullary compartment, with subsequent clone selection and escape, enabling the development of iEMR.\textsuperscript{6}

With the increased use of alternative donors, this has been contested in the haploidentical setting, with a recent report showing significantly increased rates of iEMR in patients who do not develop cGVHD. It is suggested that the role of GVL, coupled with GVHD, in this HLA-mismatched setting could partially explain the added benefit of GVHD in this subgroup. This report also evidenced increased tumor chemosensitivity in patients with EMR compared with BMR, possibly explained by reduced concentrations of conditioning therapy at EM sites.\textsuperscript{9}

Cytogenetics associated with poor outcomes and advanced disease at the time of HSCT were described as risk factors for iEMR in initial cohort studies.\textsuperscript{1,5,10,15,16} However, recent publications that include alternative-donor HSCT recipients have reported that a haploidentical source could overcome this negative impact.\textsuperscript{9}

The influence of type of conditioning regimen on likelihood of iEMR has been studied only retrospectively, mainly comparing TBI-based versus chemotherapy-based approaches. The landmark paper by Simpson et al showed a significantly elevated rate of iEMR in patients receiving busulfan-based conditioning. This finding has been related to the lack

\textbf{Figure 4} PET-CT imaging one-year post-relapse evidencing osseous lesions and lymphadenopathy.
of penetration of drugs into the immune sanctuaries with chemotherapy-only regimens.17

Multiple approaches, including combination and single treatment for iEMR, have been described. Combination therapy including systemic chemotherapy plus local radiotherapy (or in CNS disease, radiation to the craniospinal axis, intrathecal chemotherapy, and systemic chemotherapy) has been associated with higher response rates than single-treatment strategies.9 Nonetheless, the best responses have been observed when combination therapy is followed by a cellular therapy (eg, second allogeneic HSCT, donor leukocyte infusion, and donor stem cell infusion), leading to CR rates of greater than 80%.5,13 Whether this increase in CR rate translates to an increase in survival outcomes remains debatable due to conflicting results in the current literature for iEMR. ■

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FIVE KEY REFERENCES

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For references visit cancernetwork.com/iEMR-HSCT

Key Points

• Isolated EMR is defined as the presence of clonal blasts in any tissue other than the medullary compartment with a bone marrow evaluation with <5% clonal blasts and a full donor chimerism.

• Patients with iEMR have shown better survival outcomes when compared to BMR and EMR and in most cases it heralds a systemic relapse.

• Risk factors for iEMR include: younger age, history of EMD, poor risk cytogenetics, advanced disease at HSCT, development of GVHD, and non-TBI based conditioning regimens.

• Combination therapy, local and systemic, can achieve better remission rates in this subgroup of patients.
The FDA approved pembrolizumab (Keytruda) for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or chose to not undergo cystectomy. “This is a major advance,” lead study investigator Arjun V. Balar, MD, associate professor of medicine and director of the genitourinary medical oncology program at NYU Langone Health’s Perlmutter Cancer Center told ONCOLOGY. “While cystectomy is highly curative, there is a substantial impact on short and long-term quality of life with the surgery and high rates of complications as well, including an approximately 5% rate of mortality.”

The approval, which was based on findings from the phase II KEYNOTE-057 trial (NCT02625961), follows the 9-4 favorable vote in December 2019 from the FDA’s Oncologic Drugs Advisory Committee that supporting the approval of the new drug application for pembrolizumab. The FDA recommended a dose of 200 mg every 3 weeks. “This approval proves that systemic immunotherapy is active in a ‘localized’ cancer process and has ushered the development of new treatments that could be combined with immunotherapy for the further benefit of patients with this disease,” said Balar.

Pembrolizumab is the first new drug approved for BCG-unresponsive high-risk NMIBC since 1998. Prior to this approval, cystectomy was usually recommended to patients. “A substantial proportion would outright refuse the surgery, and opt for other less effective treatments, which would then compromise their care,” acknowledged Balar. “With the approval of pembrolizumab, we have an effective option after BCG which will enable more patients to safely avoid a cystectomy.”

**KEYNOTE-057 Trial**

The multicenter, open-label, single-arm, multicohort phase II KEYNOTE-057 trial enrolled 102 patients with BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors who were ineligible for or did not undergo cystectomy. “The primary efficacy outcome measure was the proportion of patients achieving a complete response (complete eradication),” Balar said.

Key secondary endpoints were duration of response and safety. In cohort A, 96 patients were administered pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or disease progression. Disease was assessed every 12 weeks, and those who did not have disease progression could receive treatment for up to 2 years. Pembrolizumab elicited a CR rate of 41.2% (95% CI, 31.5-51.4), with a median duration of CR of 16.2 months (range, 0.0 to 26.8). Nineteen (48%) of the 40 responding patients maintained their response for 1 year or more.

At an updated median follow-up of 21.1 months (range, 4.6-33.4), treatment was ongoing in 11 patients. Eighty-eight patients discontinued pembrolizumab due to persistent disease (n = 40), recurrent disease (n = 33), adverse events (AEs; n = 10), achieved CR (n = 2), physician decision (n = 1), protocol violation (n = 1), and patient withdrawal (n = 1). The most common AEs (incidence ≥10%) were fatigue, diarrhea, rash, pruritis, musculoskeletal pain, hematuria, cough, arthralgia, nausea, constipation, urinary tract infection, peripheral edema, hypothyroidism, and nasopharyngitis.

Treatment with pembrolizumab is generally very well tolerated, with up to [one-] third of patients reporting no side effects,” according to Balar. “However, clinicians should be aware that immunotherapy treatment can lead to immune-related side effects. Severe side effects from the immune system are rare, but important to recognize quickly. [Because] any organ system can be affected by the immune system, a clinician must be aware that any symptom that is new while on treatment with immunotherapy could be an immune-related side effect.”

Pembrolizumab is currently being tested in a similar population of patients in the ongoing phase III KEYNOTE-676 trial. “Specifically, [this trial] is evaluating BCG with or without pembrolizumab in patients who have persistent [high-risk] NMIBC after 1 course of induction BCG,” said Balar. “The goal is to evaluate if its use in combination with BCG further improves outcomes.”

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When the Miami Breast Conference was founded in 1983, treatment for breast cancer was mostly limited to surgical interventions and radical mastectomies. With the development of immunotherapy and targeted agents, the treatment landscape has progressed immensely, sparing many patients from what was often a debilitating and disfiguring surgery.

Prior to the 37th Annual Miami Breast Cancer Conference, ONCOLOGY sat down with Patrick I. Borgen, MD, to discuss the latest trends in surgical and medical oncology, the transformation of breast cancer treatment over the course of his career, and the role he played within that evolution.

Q: You are delivering a commentary at the Miami Breast Conference. Can you give us just a little preview of what it is going to entail?

DR. BORGEN: So right now, on the preliminary schedule I am actually going to give 2 talks. On Friday morning at the plenary session, I am going to present some work that we have done on a totally unique group of patients who unfortunately had their breast cancers missed, sometimes on a series of imaging studies. And so, by the time we saw them you could look back over time and see 1, 2, 3, 4 years of growth of a breast cancer. What it represents, and it is a sad dataset, but it represents the natural history of untreated breast cancer in the modern era with modern diet and modern stresses. And what we show is that it is completely impossible to predict the growth rate of breast cancer. In the dataset I will be presenting, the tumors are all estrogen receptor (ER)-positive (ER+). They are all negative for the human epidermal growth factor receptor 2 (HER2) oncogene. So, there should be a very homogenous population, but what we show is that it takes a complete random scattershot of how breast cancers actually grow. This has a lot of implications, for example, in the medical–legal world, where often when there is a delay in diagnosis, the parties in the action will make bold statements about how big the tumor might have been, or how big it was a year ago or 2 years ago. This falls under the head of what is called tumor doubling time, and what we show in this paper is that it is almost impossible to predict tumor doubling time. So, I think it is important. It is a piece of work we have been laboring on for about 5 years, and I am very proud to be sharing it with the Miami audience.

Q: Can you tell us a little about the second presentation?

DR. BORGEN: My second presentation at Miami in March will be on what we have done to, frankly, eliminate opioids from breast cancer surgery. So, when I got to Maimonides, which is a very large, very storied urban hospital in Brooklyn, I discovered things like we deliver 9000 babies a year. That is way more than Sloan Kettering delivers.

We have a very busy emergency department (ED). Our ED saw 120,000 patients last year. But what I learned was that we had an amazing opioid problem, with patients coming into our ED every single day from our neighborhood, and that a study showed that approximately 80% of those addicts... and victims of overdose... started with... a [physician-]prescribed narcotic.

So, about 5 years ago we got heavily involved in trying to reverse this. And there were a number of advances along the way that helped us. It really was, directly addressing a need in our community. And now it is clearly a national need.

So, I am really happy with what we did [here] in Brooklyn... we have treated over 1000 consecutive patients with a breast-conserving approach without a single milligram of opioids—over 1000 patients! So, if the rest of the country [can] come close to that, we could really make a dent in the opioid epidemic in this country.
Q: What are you looking forward to seeing presented at the conference?

DR. BORGEN: It has been another banner year in breast cancer research. During the Miami 2019...conference, the FDA approved atezolizumab (Tecentriq) as the very first true immunotherapy for breast cancer. And since that time, we’ve learned more and more about immunotherapy. I think that will be a feature of this meeting. We continue to reframe our understanding and treatment of HER2-positive (HER2+) breast cancers, and within the past year we saw approval for an antibody–drug conjugate called T-DM1 in patients who received neoadjuvant therapy in the HER2+ setting and had residual tumor burden.

We have also seen at least 3 commercially available cell cycle checkpoint inhibitors in the ER+, HER2-negative space.

And these drugs have set a new standard of care, particularly in the metastatic setting. So, part of what the story is this year continues to be a class prediction as a goal, matching the disease in front of you to the treatment you are recommending. And I think we are getting better and better at doing that. And so, the strong implication is that breast cancer is certainly more complicated to treat now than any time in history. Staying current in breast cancer is more challenging than at any previous time in history. And I think it is the role that Miami plays. I think that at Miami we pride ourselves on the practical. Our motto of “hear it Friday, use it Monday” has never been truer than right now. Virtually all of the lectures will be proceeded by a clinical case study similar to our tumor board’s back home that we do every week with very specific questions that we want the speaker to answer. And so, this is highly clinically applicable information designed for the practicing surgeon, oncologist, radiation oncologist, radiologist, and pathologist who is in the trenches diagnosing and treating breast cancer [patients] every day.

Q: You said that breast cancer is more complicated now and more difficult to treat than it has ever been. Why is that?

DR. BORGEN: I think that we have always had a sort of fundamental understanding that breast cancer was a family of diseases, not a single disease. And yet, as recently as 10 or 15 years ago, we were largely treating it as a single disease. As a deeper understanding of breast cancer has emerged, and as clearer subtypes have emerged, and as effective treatments targeting specific subtypes have emerged, it means that we have got to be much smarter in our choices. I like to say that breast cancer is no longer about seeing the clinical star, it is about seeing the star team, and I really do think that [it is] unbelievably important. For so many years we did surgery first, and then chemotherapy, and then radiation, and then hormone treatment. And very often today we change that sequence with neoadjuvant chemotherapy or neoadjuvant estrogen blockade. So, something that is as fundamental as the sequence of the treatments has really changed dramatically over the last decade.

And, of course, the agents that we have available, the immunotherapy agents, the cell cycle checkpoint inhibitors, even the poly(ADP-ribose) polymerase inhibitors that we are using in patients with BRCA1 and BRCA2 pathogenic mutations, are proving to be incredibly effective in that unique subset of patients with metastatic breast cancer. So much so that virtually every patient who has metastatic breast cancer now gets tested routinely for BRCA1 and BRCA2. So, it’s a more complicated horizon. But the glass is clearly half full and not half empty, because patients are doing better than they have ever done before. Survival rates continue to increase, and that increase is accelerating. So, the future is incredibly bright.

Q: How has the Miami Breast Conference changed over the years?

DR. BORGEN: When Dr Dan Osmund founded the meeting in the early 1980s, there really was a single flavor, if you will, of chemotherapy that was not really commonly used at that point. Mastectomy was the most common operation. Estrogen blockade with tamoxifen was around but not popularized. It
was 10 years before screening mammograms became popular. And so really it was almost purely a surgical meeting. And if you fast-forward to today, 34 [or] 35 years later, our audience is about 60% surgeons, but the other 40% is vitally important, and really rounds out the team, because today it is impossible to treat this disease without a true multimodal approach.

Q: What are the major trends in surgery and medical oncology right now?

DR. BORGEN: I think all of the exciting work that is being done is in the neoadjuvant space, whether it is neoadjuvant chemotherapy, or neoadjuvant hormonal therapy, or neoadjuvant endocrine therapy. And what is happening is…very often we are able to downsize the magnitude of surgery, the disfigurement of the surgery, the disability of the surgery, and I think that is the most exciting trend in breast cancer for the surgeon that is out there today. We are doing more, we are doing smaller yet more sophisticated operations because patients are receiving medical therapy first.

Q: How did you wind up in medicine?

DR. BORGEN: My father, interestingly enough, worked for the National Aeronautics and Space Administration. He was part of the team that built the very first stage of the Apollo Saturn V rocket. The massive rocket that lifted the whole thing off the ground was built in New Orleans, and so I grew up in New Orleans. My mom was a schoolteacher and my dad was literally a rocket scientist. I initially wanted to be an engineer, really wanted to follow in his footsteps. And so, I studied engineering as an undergraduate at Tulane University and did not love it. And my heart kept coming back to medicine. So, at the end of my engineering degree at Tulane I applied for medical school, and lo and behold I got in and attended Louisiana State University (LSU) School of Medicine. And I have never looked back.

I have always been extremely happy about my decision to pursue medicine. The idea of being part of a decision-making process, an intervention process at a critical moment in another human’s life, was really attractive to me. I wanted to make a difference. I wanted to, on an individual basis, make a difference. And I love people. And I think I have always had above-average people skills. And so that was really the attraction to medicine.

Q: What attracted you specifically from medicine to oncology?

DR. BORGEN: When I was a resident in surgery in New Orleans, a lot of what we did was trauma. And I did a fantastic number of operations for gunshot wounds and knife wounds. It was a huge part of training in surgery in New Orleans at the time. And as exciting as it was, it was not really intellectually stimulating. So probably as a result of my, you know, kind of deep trauma experience, I wanted to be able to study a disease, I wanted a common disease. I wanted a disease [in which]...discoveries could make a difference in a big way.

There were only a few tumors that fit the bill, and breast cancer was by far the most common and by far the least well understood in the late [19]80s. We were still doing radical and modified radical mastectomies. A quarter of our patients were dying. There were huge side effects from the surgery, it was debilitating and disfiguring and defeminizing. And so, once I decided on surgical oncology, the choice for breast cancer for me was easy. It was the most interesting, least well-understood disease that was out there.

Q: You have talked about your mentor Murray Brennan and how much respect you have for him. His saying is always: adulation is soporific. And you have also talked about the importance of being self-critical. So, in all that, how do you find the way to celebrate your success?

DR. BORGEN: That is a great question. I believe that I have never accomplished anything by myself. I believe that I have assembled teams. I have motivated teams. I have supported teams. So, our victories have always been group celebrations. And that was true at Memorial Sloan Kettering; it is true here in Brooklyn. You assemble the right team, you give them the resources they need, and then you stay out of their way. But I do not feel as strongly as Murray did about adulation being soporific. I think that...
I think our job is to provide the facts, to provide our best guess about where the field is going, and then help the patient find the solution that is right for them.

-Patrick I. Borgen, MD

This new generation of what have been called millennial(s) that are coming into medicine are wonderful. But the truth is they respond really, really well to positive reinforcement, more so than my generation did.

And so I think I have had to change my style to fit the new generation of cancer surgeons and cancer researchers, and I am very comfortable in that, and I laugh now when I think about, you know, Dr Brennan and the wonderful... impression that he made on me. But it would have been nice every once in a while, [for him] to say, “that a boy!”

And you know I have stayed very close to Dr Brennan and we have dinner 3 or 4 times a year, and I bust his chops about this now that I am of a certain age and do not fear him. I give him a really hard time and he laughs. He is funny about it. I think he was the greatest cancer surgeon of the 20th century, and I think history will... reflect that. But he got there by being really tough on himself, so I have emulated that to an extent, but I think I have softened my act over the years. I do not think I am the tough SOB that... I used to be.

Q: What was it that initially brought you to New York?
DR. BORGEN: I went to Tulane [as an] undergraduate and I went to LSU medical school, and then I trained at a wonderful surgery program called the Ochsner Clinic in New Orleans. And really, I fully believed that I would practice as a surgeon in New Orleans. I wanted to do a little more training, so sort of through a friend of a friend I contacted a guy named Dr Michael Osborn who ran the Breast Cancer Research Laboratory at Memorial Sloan Kettering.

And I got him on the phone, he had a thick British accent and I said, “Look, you do not know me, but we have a mutual friend, and I will come work for free.” And he said, “When can you show up?” And so, I took out a $20,000 bank loan, and I went to New York, and I worked for free for 1 year. And they decided to keep me, and they actually paid me for my second year there, which was nice. And then the following year I was offered a spot on the faculty, the surgical faculty, on the breast service at Memorial Sloan Kettering. Then 2 years later [I] became the chief of the division. So, it was a very magical time for me.

Q: Was it just the opportunity to practice at Memorial Sloan Kettering that attracted you to New York?
Q: When you started at Memorial Sloan Kettering, the institution was doing BRCA research. Were you a part of that?
DR. BORGEN: Yeah, I hit the 2 years in the breast cancer research laboratory under the direction of Dr Michael Osborne. And Dr Osborne left to pursue other career pathways. And when he left there was a gap. The institution asked me to take over... the leadership of the lab, which I certainly embraced. That played a strong role in me deciding not to go back to New Orleans and to stay in New York.

And so, we were deeply involved. The structure of BRCA1 was discovered about a year after I started as an attending [physician], and we had an enormous population of patients to begin studying, and a few years later we discovered the founder effect mutation on BRCA2. And that was really a clinically important, practical discovery, and that sort of launched us.

Q: And you personally, you were at the forefront of HER2 research, correct?
DR. BORGEN: Very much. We had one of the world’s first cell lines that had amplified HER2. And so, we were able to do experiments in vitro outside of the body, learning about the form and function of the HER2 oncogene. And so, we did a lot of the early work on HER2.

Q: So how does a surgeon wind up doing so much molecular research and genetic research?
DR. BORGEN: I think that as a young surgeon I was convinced...
that surgery would not be the long-term answer. When you think about those first patients who were found to have BRCA1 mutations, and they said, “Doc, what can I do about this?” and we said, “Well, we can remove those breasts,” and they looked at you like you were crazy. I think no one who really thought this through back then felt that the future of prophylaxis would be radical surgery. And so, the answer had to be medical, it had to be genetic, it had to be genomic. So, I think early in my career I was convinced that surgery would play an important but diminishing role into the future.

Q: Over time, breast cancer treatment has been moving towards less invasive therapy. But more and more high-risk women—women who are BRCA-positive—are choosing prophylactic mastectomy. How do you counsel your patients when they come to you and say they want a double mastectomy?

DR. BORGEN: First of all, I think that it is purely a patient choice, not a doctor choice. I'm not so sure—I do some consulting for a big healthcare system here in New York and they have data on tens of thousands of patients, and it really looks like double prophylactic mastectomy is maybe less common than it was 10 years ago. And part of that is the advent of better screening of breast magnetic resonance imaging [and] 3-dimensional mammography.

In the [19]90s when mammograms were analog, there was a 40% false-negative rate [in] mammography for BRCA1-associated breast cancer. And so those numbers just did not add up. If you had a 70% chance of getting breast cancer and a 50% chance that a mammogram would miss it, then clearly you were likely to choose what Angelina Jolie chose,...a double mastectomy. In today's age of much better imaging, I think that we see less patients selecting to undergo risk-reducing mastectomy.

But at the end of the day, I give my patients as much of the story as I think I can. I feel that my role is to develop a relationship with them, so that I can help them make the decision that is right for them. But the worst thing in the world for a breast surgeon would be to have a patient say, “I regret doing this operation. I regret,...a double mastectomy.” So, I think our job is to provide the facts, to provide our best guess about where the field is going, and then help the patient find the solution that is right for them.

You know there are very, very anxious—understandably anxious—patients who have seen relatives die of breast cancer who come in and say, “Forget it, I want both breasts removed,” and of course we do the operation. And then there are patients that are less certain and decide to take other courses. So, I really think this is an era where we are offering, but not selling risk-reducing mastectomy. I think that is important.

Q: You have also done a fair amount of research in male breast cancer. What is the biggest difference in treating male versus female patients with breast cancer?

DR. BORGEN: You are right. I [have] published [results from] a number of studies. I recently[saw] the very first male who had synchronous bilateral breast cancer. And he presented with just a drop of blood from 1 nipple. A very astute internist saw it and said to me “we got a mammography,” and lo and behold he had bilateral breast cancer. And...we learned later he was a BRCA2 mutation carrier. The risk of it [breast cancer] is significantly increased in BRCA2 mutation carriers who are men.

So, we continue to treat male breast cancer very similarly to how we treat female breast cancer. Because of the rare nature of the disease, we have to extrapolate from trials of female breast cancer. And...that has been effective. Men do respond very, very similarly to the treatments that have been developed for women. So, the chemotherapy is really identical. The estrogen blockade with tamoxifen is identical. The role of radiation is identical. The biggest difference is that, I would say 98% of the...
time, male breast cancers are below the nipple. We are still doing a lot of mastectomies. Breast conservation [in men] is not nearly...as common as it is in female breast cancer. That is actually the biggest difference right now.

Q: Of all the research that you have done in your career, and obviously you have done a lot of it, what do you think has been the most important or the most impactful?

DR. BORGEN: In the surgical arena, I think working towards kinder, gentler approaches to breast cancer has been the theme of my entire career. I was there for [the] transition from mastectomy to lumpectomy, from mastectomy to breast conservation therapy. We played a significant role in the design, development, and popularization of sentinel node biopsy. At the time, the largest US trial had about 3000 patients. We had done 6000 of the procedures. The development of nipple-sparing mastectomy was reconstruction, [and] we were there at the very beginning of that. In patients who [chose] or choose a mastectomy, this is a way to soften the blow of a very, very disfiguring operation. And so, I think the theme of my career has...been looking for a kinder, gentler way to treat the disease.

Q: Let us talk about racial disparity in outcomes. Black women are 14% more likely to die from breast cancer. What can be done just to close that disparity?

DR. BORGEN: It is a great question and it is 100% true. In Brooklyn...where screening remains a challenge, we have had a number of outreach programs to schools, to churches, to congregations to encourage screening. Through various foundations we offer prescreenings. But it is more than just screening. It is more than just early detection, and we know that both African Americans and Caribbean Americans have a higher likelihood of getting triple negative breast cancer. And more research needs to be done to fine-tune our understanding of different subsets of triple negative breast cancer. We have been treating triple negative breast cancer, particularly in African American and Caribbean American patients, as a single disease entity. And it is not. It is a small family of diseases in and of itself.

Now, I think the approval of atezolizumab as the very first immunotherapy in breast cancer, which is being used in metastatic, triple-negative breast cancer, will save hundreds of lives of African American women. And I think we will begin to see progress in that area.

Q: Is part of it getting more African-American women to participate in clinical trials?

DR. BORGEN: It definitely is. When I was at Memorial Sloan Kettering, we built a breast center, it was called BECH—Breast Evaluation Center of Harlem. And it was a screening facility on 125th Street in Harlem that offered low or no-cost mammograms. And a lot of the community did not always trust Memorial. Some women felt they were being [used as] guinea pigs in some experiment. Of the women who had a first mammogram, only about [one-] third ever came back for a second mammogram. So clearly there were cultural impediments that we did not understand. And when the National Surgical Adjuvant Breast and Bowel Project started the world’s first breast cancer prevention trial, we offered participation in that trial at the Breast Evaluation Center of Harlem.

But the community leaders cautioned us that it might further decrease some behaviors of women seeking treatment, that it might further make women feel that they were being guinea pigs. Those differences persist today, and we have to have more broad-scale representation in our clinical trials.

Now, I am in Brooklyn, which is a real melting pot. Our Patient Bill of Rights is in 43 languages. And...we have extremely broad participation in clinical studies that we are doing. So, ...one of the joys of working in Brooklyn right now is that we really are able to offer clinical trial participation across a more normal slice of America if you will. I think Brooklyn is a great microcosm of what America is about today. And so that has been exciting.

Q: You mentioned that you are in Brooklyn now. It is a very diverse area. How do those cultural differences play out in sort of the day-to-day treatment at Maimonides?

DR. BORGEN: What lured me away from Sloan after 20 years was to become part of a group to build the very first cancer center in the history of Brooklyn. And even though...our center is about...10 miles from where Sloan Kettering is, we have a largely underinsured and uninsured population. And [many] of those patients can not really go to the Sloans of the world, and so you had this amazing giant, the fourth largest city in America, in the shadow of Manhattan, literally, lacking cancer services.

So, the challenges have been many. Language. There are times [when] we have to use...
2 interpreters; for example, Fukienese, to Mandarin, Mandarin to English. So, you are in a room with a patient with 2 different interpreters. So, transmitting complex information is a challenge. It is also the joy of the job. It is also providing... services to a group that 10 years ago did not have these services.

Q: Memorial Sloan Kettering is the top 1%, the pinnacle of cancer research. So, what was it about getting to work in Brooklyn that drew you out of that gilded tower?

DR. BORGEN: Yeah, I did not grow up in a gilded tower. My parents combined income in 1968 was $25,000. They were both happy. They both loved their jobs. And they were both very fulfilled [with] their jobs. And so, I knew having started at Sloan at a very young age that I really wanted to finish my career going back to an underserved area. And I looked in Louisiana, and I looked in Appalachia, and looked all across the country. And someone said, “Have you ever been to Brooklyn before?” And I said, “Yeah. I’ve been to Peter Luger’s Steak House twice in Brooklyn.”

And of course, as I started to research Brooklyn, I understood that it was 3 million people with no cancer services. In fact, there were no members of cancer societies living in Brooklyn. So, I really had a chance to go back to my roots, which is how I see this Brooklyn experiment, and it was just an unbelievably wonderful opportunity for me.

One of my friends told me that I went from doing well to doing good. And maybe that is true. But I love what we are doing here in Brooklyn, and I may have changed Sloan Kettering a little bit over my 20 years. I like to think I changed it a little bit. But I know I have changed Brooklyn an enormous amount, and that really feels... very satisfying.

Q: You lead a training program in Brooklyn. Tell me a little about that. What are you looking for, and what do you want your trainees to take away?

DR. BORGEN: We have over 500 residents and interns in our hospital. We have about 50 or 60 in surgery. And as we recruit trainees, we are looking for... empathy, community service, diversity. We want physicians and athletes and authors and painters. We want as diverse a person as we can find, cause frankly those diverse individuals by far make the best surgeons. So, it has been an evolution.

I have actually run this training program for 10 years now; and I am really proud of the surgeons that we are graduating. They are doing extremely well, and I think they are going out and emulating this program across the country, really. Surgeons have a bad reputation of being butt holes, and sometimes it is true. And we do not think surgeons need to be. We think surgeons who are, often in breast cancer, the quarterback of the team. [They] need to be kind and gentle, and really smart, and really empathetic, and I think that is what we are achieving.

Q: You have also taken a bit of a different approach to recruiting your team at Maimonides. Can you tell me a little about that and what you are looking for in a physician?

DR. BORGEN: I think that academic medicine almost universally puts a premium on academic productivity, how many publications, how many presentations, what is your national reputation? And certainly, I did that when I was recruiting at Sloan. But as I matured, I sort of realized that smart was relatively easy; nice was not always so easy. And as I was building my team here in Brooklyn, we recruited for values first, for emotional IQ first, empathy first, and then looked at somebody’s credentials. And what we found was that it was really difficult.

It was hard to find, but they were out there. But you had to look, you had to start with values and then once you established what you believed someone’s values were, then look at their ability, and that has made all the difference. I recruited about 80 surgeons to Brooklyn in my role as the chairman of surgery. And it has created a culture that doctors want to practice in. I get calls every day from physicians saying, “Gee, I hear you’re doing something really interesting in Brooklyn, I’d like to come take a look.” And, of course we say, “Come take a look.”

What we have created is a work environment that is very different than most academic institutions, where there is comradery, there is collegiality, there is mutual support, there is professionalism, there is transparency.

-Patrick I. Borgen, MD

So, what we have created is a work environment that is very different than most academic institutions, where there is comradery, there is collegiality, there is mutual support, there is professionalism, there is transparency. People are self-critical. Murray Brenner would be so proud because people are self-critical. We have our morbidity and mortality conferences and the first thing the surgeon says is, “Let me tell you what I did and what I would do different next time,” and that makes all the difference.

And so, I think that whole fundamental concept of...in medicine, insisting on nice and excellence is a game changer. There is a lot of institutions that take good care of patients. And,...our country is blessed to have thousands of those frankly. But the number of institutions that do that and make a patient feel well cared for is pretty rare, and that is what I think we do in Brooklyn.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
79-year Old Man on Nivolumab with Itchy Erythematous Patches

By Mehmet Sitki Copur MD, and Susan Corey, MD
Mary Lanning Healthcare Morrison Cancer Center and Grand Island Dermatology

PRESENTATION

A 79-year-old white man presented with an ulcerated chest wall lesion developing from an existing mole. After definitive surgery, it proved to be a malignant melanoma and staged as T4N1M0. He received 1 year of adjuvant therapy with nivolumab. Starting on the last month of adjuvant nivolumab treatment, he developed itchy erythematous patches on his left posterior shoulder that spread over his trunk, arms, and thighs (Figure 1). Gradually, he began to develop more urticarial pink plaques, tense bullae, and erosions in the same locations. There was no involvement of mucosal surfaces. Punch biopsy of 1 of these lesions was performed and sent to pathology for evaluation by hematoxylin and eosin (H&E) staining and direct immunofluorescence (DIF).

What is your diagnosis?

A. Recurrent malignant melanoma
B. Erythema multiforme
C. Drug rash
D. Bullous pemphigoid

TURN TO PAGE 54 for the answer and a discussion of this case by experts.
IMMUNOTHERAPY

CORRECT ANSWER: D. Bullous pemphigoid

Continued from page 53

Immunotherapy is associated with a unique set of immune reactions known collectively as immune-related adverse events (irAEs). Cutaneous toxicity is among the most common irAEs in patients treated with immunotherapy. Although often mild, dermatologic toxicity can occasionally be high grade and potentially life-threatening. In cancer patients treated with immunotherapy, physicians should have a greater index of suspicion for cutaneous irAEs. Bullous pemphigoid is an autoimmune subepidermal blistering disease characterized by the development of tense bullae. It is most frequently seen in the elderly. The skin lesions and biopsy results of this patient are consistent with bullous pemphigoid. H&E staining showed perivascular lymphocytic and eosinophilic infiltrate. DIF revealed linear immunoglobulin G and complement component 3 along the basement membrane zone. Programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1)-induced bullous pemphigoid has recently emerged as a potentially serious dermatologic toxicity and has been observed with some degree of frequency. There is no standardized treatment algorithm for management of PD-1/PD-L1 inhibitor-induced bullous pemphigoid, but patients frequently require topical and systemic steroids.1

REFERENCE

For more quizzes, go to cancer-network.com

Figure 2 x20 Magnification (A), x100 Magnification (B), x400 Magnification (C).
Synchronous Bilateral Lung Cancer With Discordant Histology

Mehmet Sitki Copur, MD, FACP; Rudy Lackner, MD, FRCP; Whitney Wedel, MD; Nikki Lintel, MD; Mathew Stritt, MD; and Kalpesh Gnatra, MD
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Case
A 70-year-old white woman with a 40 pack-year history of smoking has been on follow-up for previously detected abnormal lung nodules during the past 3 years. The most recent computed tomography (CT) scan revealed an increase in the size of the left upper lobe nodule—from 4 mm a year ago to 2 cm on the current CT scan. A CT-guided needle biopsy of this nodule revealed small cell lung carcinoma (Figures 1A and 1B). Further work-up with a positron emission tomography (PET) scan confirmed the left upper lobe lesion with a standard uptake value (SUV) of 12.7, and also revealed a right upper lobe nodule (1.1 cm in size) with an SUV of 2.1 (Figures 2A and 2B). Following multidisciplinary evaluation at the thoracic oncology tumor conference, the patient underwent initial bronchoscopy with ultrasound (endobronchial ultrasound [EBUS]) and biopsy of lymph node levels 10, 7, and 4, followed by a right-sided video-assisted thoracoscopic surgery (VATS) and a wedge resection of the right upper lobe nodule, and a left upper lobe lobectomy. (Figure 3). Mediastinal lymph node dissection revealed no lymph node involvement. Pathology of the right upper lobe wedge resection revealed a 1.3-cm non–small cell lung adenocarcinoma, and pathology of the left upper lobe lobectomy revealed a 2.5-cm small cell lung carcinoma (Figures 4A and 4B). Both tumors had visceral pleural involvement and were resected with clear margins. The right upper lobe tumor was staged as pT2N0 and the left upper lobe tumor was staged as pT2N0 (per the 8th edition of the American Joint Committee on Cancer staging system).

Introduction
Lung cancer is the second most common cancer in both women and men (excluding skin cancer) and the leading cause of cancer-related death in both sexes. Occasionally, patients with a typical clinical presentation of lung cancer may exhibit a second lesion with similar appearance at initial presentation or later. Since first described in 1924 by Beyreuther, synchronous multiple primary lung cancers (SMPLCs) have been associated with a poor prognosis. Subsequent studies of SMPLCs have been difficult to interpret due to a small number of cases and little information regarding the tumor...

ABSTRACT: Synchronous multiple primary lung cancer (SMPLC) is a rare occurrence affecting 0.5% to 2% of patients with lung cancer. Synchronous discordant histology with small cell and non–small cell lung carcinoma is an even less common entity. There have been several presentations of synchronous or metachronous multiple primary lung cancers in the literature. However, reports discussing treatment options and prognosis in patients with SMPLC of discordant histology with small cell and non–small cell carcinoma in the same patient are scarce. We report a case of SMPLC presenting with a limited stage left upper lobe small cell lung cancer and an operable right upper lobe non–small cell lung adenocarcinoma. Diagnostic, surgical, and medical treatment options for the patient along with a review of SMPLC topics are presented.
characteristics and stage. SMPLCs are presumably uncommon; however, its true incidence seems to be increasing as a result of the widespread availability and use of early detection tools such as multislice spiral CT, PET, advanced interventional radiology, and thoracic surgery techniques. It is important to determine whether the multiple lung lesions are metastases or separate primary lung tumors. Traditionally, multiple primary lung cancers have been defined by the clinical criteria initially developed by Martini and Melamed in 1975, refined later in 1995 by Antakli et al, and more recently updated in 2007 by the American College of Chest Physicians (Table 1).3-6 Multiple primary lung cancers can present as synchronous or metachronous cases with concordant or discordant histology.7 The incidence has been reported to be approximately 1.5% to 2% per patient per year but true incidence may be as high as 20%.8,9 The majority of tumors classified in this way have revealed the same histologic type with similar survival results regardless of the histologic type, suggesting that the traditional definition of second primary lung cancers based on clinical features may be acceptable.8 As more information including genetic and molecular analyses of lung cancer is becoming available, accuracy of this diagnosis may improve and can mitigate the problems of differential diagnosis.

Diagnostic Considerations

It is essential to determine the histology of the lung tumor. Infection and other benign diseases, such as inflammatory granulomas, must be ruled out. Non-small cell lung cancers (NSCLCs) display a variety of morphological and molecular features. Accurate subtyping has been shown to predict response rates and toxicities of specific drugs as well as patient survival. Assessment of multifocal lung tumors and the distinction of synchronous primary tumors from intrapulmonary metastases is crucial in determining the staging of these tumors and subsequent treatment approaches. The reported frequency of multiple anatomically separate lung tumors with the same histology ranges from 0.2% to 8% in patients with NSCLC. The majority of these cases seem to be clonally related.10-13 Distinguishing SMPLC from intrapulmonary metastases originating from a single pulmonary neoplasm or other neoplasms in different organs can be challenging. Careful clinical as-

![Figure 1 CT-guided needle biopsy, left upper lobe: small cell neuroendocrine carcinoma (H&E, 400X magnification) (A). Immunoperoxidase stain for synaptophysin (400x magnification) (B).]
essment along with utilization of recent advances in imaging, surgical, and pathological techniques, and ultimately the use of genetic and molecular analyses, may offer valuable resources in evaluation and differentiation of SMPLCs from metastatic lesions.

In addition to identifying the morphological characteristics of subtypes of NSCLC and small cell neuroendocrine tumors, immunohistochemical staining for cytokeratin (5, 6, 7, and 20), p63, thyroid transcription factor-1, chromogranin, synaptophysin, and Ki-67 have been widely utilized as initial diagnostic tools. While the diagnosis of SMPLC with different histologies may be straightforward, distinguishing second primary lung cancer versus intrapulmonary metastasis in synchronous tumors of the same histology can be hard. The ability to determine the clonal origin of SMPLC may be essential in differentiating between the possibility of a single clonal event resulting in a tumor with subsequent spread into other parts of the lungs versus multiple independent tumors arising in an area due to a common carcinogen exposure or a genetic predisposition. To address this challenge, different molecular approaches have been explored. Currently, this is an area of ongoing research. In a series of 14 patients with synchronous NSCLC, Shimuzu et al reported a clonal relationship in 11 (79%) of cases by analyzing the loss of heterozygosity (LOH) and p53 mutations.14 Similarly, Wang et al documented a clonal relationship in 77% of 30 patients with multifocal lung tumors utilizing LOH, p53 mutations, and X chromosome inactivation status.15 More recently, Warth et al evidenced that at least 64% of patients with synchronous multiple primary NSCLC had a clonal relationship by utilizing a combined assessment of LOH (using a panel of 14 polymorphic microsatellite markers) and KRAS and endothelial growth factor receptor mutations.16

Local Treatment Options
Although some criteria have been defined for diagnosing multiple lung cancers, no definitive guidelines for the selection and treatment of patients with this presentation are currently available. Pretreatment workup should focus on excluding any extrathoracic disease and select the fit candidates for multidisciplinary management. When patients with SMPLC present with identical histology, in the absence of easily avail-
able and reliable genetic and molecular markers to differentiate between second primary lung cancer versus isolated pulmonary metastatic disease, management decisions will be challenging. It will be difficult to reconcile 2 opposite treatment approaches; for example, any resectable disease should be removed in multiple primary lung cancer, whereas surgery is futile in metastatic lung cancer. Unless a pneumonectomy or bilateral lung resection is required, which would limit cardiopulmonary reserve, curative resection can be attempted for multiple primary lesions in the same lobe or in the same lung.

However, treatment of multiple lung cancers will more likely depend on the status of the lymph nodes and whether the patients are symptomatic or at high risk of becoming symptomatic.17-20 Some of the multiple lung nodules detected on CT scans can be followed with imaging, whereas others need to be biopsied or excised. All patients should be evaluated in a multidisciplinary tumor conference involving experts from radiology, pathology, pulmonology, surgery, and medical and radiation oncology. For patients with early-stage SMPLC who are eligible for definitive local therapy, parenchymal-sparing resection is preferred. VATS is a minimally invasive surgical technique and it is a reasonable option depending on the number and distribution of lung lesions in patients with adequate lung volumes. With annual CT screening on the rise, more and more early-stage tumors are being detected and treated with curative-intent surgery as appropriate for their stage. Because the risk of lung cancer is a continuous threat in patients with prior heavy tobacco exposure for the remainder of their lives, preservation of the pulmonary parenchyma becomes a very crucial surgical consideration. Recent surgical series reports have supported the value of limited VATS resections as an important consideration. In addition, the original practice of 3 access ports in a “baseball diamond” pattern has been modified to suit operational needs, and has gradually developed into next generation approaches, including needlescopic and 2-port VATS.21 For patients with limited lung function, stereotactic ablative radiotherapy (SABR) is an option and has become a treatment choice.17, 20, 22

Provided that there is a multidisciplinary and appropriate selection and evaluation process in place, most patients with SMPLC benefit from the local treatment options of surgery and/or SABR. In a single-institution experience, Trouss et al reported surgical outcomes in 125 consecutive patients with SMPLC. Tumors were bilateral (n = 34) or unilateral (n = 91) and optimal surgical treatment was possible in 65.6% of the cases. Two- and 5-year overall survival rates were 61.6% and 34%, respectively, with a median survival of 35 months. Bilateral disease, location in the same lobe, and pN0 disease were favorable factors.23 A limited resection has been associated with increased local recurrence rates (up to 15%) in several studies when a more extensive surgical procedure is not possible due to compromised pulmonary function.24, 25 The Lung Cancer Study Group reported higher locoregional recurrence after wedge or segmental resection compared with lobectomy.26 However, overall survival rates in these studies were not sig-

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<td>MULTIPLE PRIMARY LUNG CANCERS</td>
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<td>Same histology, tumor in different lobe as primary and no N2 or N3 involvement and no systemic metastases.</td>
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significantly different, so limited resections are often preferred because they allow major conservation of lung tissue.

Similar outcomes have been reported after SABR and surgical treatment for early-stage NSCLC. The feasibility, safety, and efficacy of this approach have been well established and it is now considered a standard of care for patients with medically inoperable lung cancer. In studies evaluating the role of SABR in early-stage multiple primary lung cancers, median overall and progression-free survival rates comparable to surgical treatment were reported. However, in these studies, most patients with synchronous or metachronous lung cancer who underwent SABR were ineligible for surgery.

Our patient had bilateral upper lobe disease, underwent initial bronchoscopy with ultrasound (EBUS) with biopsy of lymph node levels of 10, 7, and 4, a right-sided VATS wedge resection for adenocarcinoma on the right upper lobe, and a left upper lobe lobectomy for a small cell neuroendocrine tumor on the left side along with mediastinal lymph node dissection. Both tumors had visceral pleural involvement, but they were resected with clear margins. All mediastinal nodes were negative.

Systemic Treatment Options
Similar to the lack of definitive guidelines in detailing recommendations for the local treatment of patients with SMPLC, there are no established guidelines for the adjuvant or systemic treatment of this entity. Most reports suggest that patients received no additional therapy after complete resection or local therapy. Finley et al reported results of 175 patients who underwent surgical resection for SMPLC. Twenty-five patients (14%) were given adjuvant therapy; 17 underwent chemotherapy and 8 received external beam radiotherapy. It is difficult to conclude the value of adjuvant therapy because of the small numbers of patients and the retrospective nature of these data.

National Comprehensive Cancer Network (NCCN) guidelines recommend observation for patients with T2a-bN0 NSCLC after curative-intent surgical resection with a clear margin. However, postoperative adjuvant chemotherapy is a category 2A recommendation for patients with T2a-bN0 tumors and negative surgical margins who have high-risk features such as poorly differentiat-
ed histology, lymphovascular invasion, wedge resection, tumors larger than 4 cm in size, visceral pleural involvement, and unknown nodal status. Right upper lobe adenocarcinoma necessitating wedge resection in our patient meets the high-risk criteria for adjuvant chemotherapy based on visceral pleural involvement and wedge resection.

Based on the NCCN guidelines, all patients with small cell lung cancer require systemic therapy as an essential component of their treatment. Adjuvant chemotherapy is recommended for patients who have undergone surgical resection or SABR for early-stage disease. Pathologic mediastinal staging for early clinical stage small cell lung cancer determines the necessity of adding chest radiation therapy. If mediastinal lymph nodes are negative (N0), systemic adjuvant chemotherapy with etoposide and cisplatin is recommended. If mediastinal nodes are positive (N1), adjuvant chemotherapy with or without concurrent or sequential radiation therapy is a category 2A recommendation. If mediastinal nodes are positive (N2), then chemotherapy with concurrent or sequential radiotherapy is a category 1 recommendation.

Our patient had a small cell carcinoma with negative mediastinal nodes but there was lymphovascular invasion and visceral pleural involvement. Adjuvant chemotherapy with or without concurrent radiation might be considered depending on her performance status. Prophylactic cranial radiation is also a consideration after completion of systemic therapy.

Conclusions
The differentiation between multiple primary lung cancers and intrapulmonary metastases is crucial for accurate staging and management of SMPLC. The arbitrary nature of the conventional histomorphological criteria and lack of well-established diagnostic and treatment guidelines make management decisions in these patients somewhat difficult. Implementing genetic and/or molecular testing criteria for accurate identification of these tumors could provide more valid information for definitive diagnosis and may guide accurate treatment decisions. Surgical treatment is beneficial for selected patients with multiple primary lung lesions and may offer long-term survival, provided that the clinical stage of the second tumor and the patient’s cardiopulmonary reserves permit it. Postoperative surveillance with medical history, physical examination, and imaging studies is mandatory to monitor for recurrence of the original tumor or screen for potentially curable, early-stage metachronous cancers.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

FIVE KEY REFERENCES

For full reference list visit cancernetwork.com/BilateralLungCancer

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Multiple studies showed improved patient outcomes and increased quality of life (QOL) among various treatments that previously demonstrated clinical benefits. These patient-centric findings, along with a promising new combination therapy for patients with advanced hepatocellular carcinoma (HCC) highlight some of the latest research to come out of the 2020 Gastrointestinal Cancers Symposium, held January 23-25, in San Francisco, California.

**Quality of Life Assessment in the BEACON CRC Trial**
Results from the phase III BEACON CRC study demonstrated that patients with BRAF V600E-mutant metastatic colorectal cancer treated with encorafenib (Braftovi) plus cetuximab (Erbitux), with or without binimetinib (Mektovi), reported substantial improvement in QOL when compared with either of the two current standard-of-care regimens of irinotecan (Camptosar) with cetuximab. Four QoL instruments were utilized in the study: European Organisation for the Research and Treatment of Cancer QOL Questionnaire (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Colorectal (FACT-C), EuroQoL 5D-5L (EQ-5D-5L), and Patient Global Impression of Change (PGIC). Reduction in the risk of QOL deterioration was estimated at 45% (hazard ratio (HR), 0.55; 95% CI, 0.43-0.70) and 44% (HR, 0.56; 95% CI, 0.44-0.71) in the EORTC QLQ-C30 and FACT-C assessments, respectively, for the triplet therapy, compared with the control arm. Moreover, the reduction in risk of QOL deterioration was estimated at 46% (HR, 0.54; 95% CI, 0.43-0.69) and 43% (HR, 0.57; 95% CI, 0.45-0.72) in EORTC QLQ-C30 and FACT-C measures, respectively, in favor of doublet therapy. The investigators observed similar results in the EQ-5D-5L and PGIC assessments, with no overall differences in QOL shown between triplet and doublet therapy across all 4 instruments.

These findings were a secondary endpoint in the BEACON CRC trial. Results from the prespecified interim analysis were previously published in the *New England Journal of Medicine,* and demonstrated an increase in median overall survival (OS) versus the control arm in both the triplet (9.0 months vs 5.4 months) and doublet (8.4 months vs 5.4 months) regimens.

At the symposium, Scott Kopetz, MD, PhD, associate professor of gastrointestinal medical oncology at The University of Texas MD Anderson Cancer Center in Houston said: “We recognized that safety doesn’t always capture the patient experience and that is the rational for incorporating QOL metrics into the study. This is an important component that really helps to understand the patient experience and complements the clinical efficacy endpoint.”

**Patient-Reported Outcomes in the IMbrave150 Trial**
Combination treatment of atezolizumab (Tecentriq) plus bevacizumab (Avastin) led to significantly better patient-reported outcomes than current standard-of-care treatments.
ported outcomes than treatment with sorafenib (Nexavar) in patients with unresectable hepatocellular carcinoma (HCC).³

Of the 501 patients enrolled in the phase III IMbrave150 trial, at least 92% completed the EORTC QLC-C30 and the HCC-specific EORTC QOL Questionnaire (EORTC QLQ-HCC18) during treatment. Delays in median time to deterioration (TTD) were reported in QOL (11.2 months vs 3.6 months; HR, 0.63; 95% CI, 0.46-0.85), physical functioning (13.1 months vs 4.9 months; HR, 0.53; 95% CI, 0.39-0.73), and role functioning (9.1 months vs 3.6 months; HR, 0.62; 95% CI, 0.46-0.84).²

Median TTD was also delayed for several disease-related symptoms, including appetite loss, fatigue, pain, and diarrhea for the atezolizumab/bevacizumab combination versus sorafenib.

The findings, along with previously published data indicating significant improvements in both OS and progression-free survival (PFS), lend support to establishing an atezolizumab/bevacizumab combination versus sorafenib.

The cohort data presented at the symposium is the first report of efficacy and safety of nivolumab and cabozantinib, with or without ipilimumab.

Seventy-one patients with advanced HCC were randomized to receive the nivolumab/ipilimumab/cabozantinib regimen (n = 35) or a doublet therapy of nivolumab combined with cabozantinib (n = 36). Investigator-assessed objective response rate (ORR) for the nivolumab/ipilimumab/cabozantinib arm was 29%, with a disease control rate (DCR) of 83%. Median PFS was 6.8 months (95% CI, 4.0-14.3), while the median OS had not yet been reached (95% CI, 15.1-not reached).³

For patients with advanced HCC who received the doublet therapy of nivolumab plus cabozantinib, the investigator-assessed ORR was 19% and the DCR was 75%; median PFS was 5.4 months (95% CI, 3.2-10.9) and median OS was 21.5 months (95% CI, 13.1-not reached).³ No new safety signals were observed in either arm.

“Patients with advanced liver cancer need new and effective treatment options,” lead investigator Thomas Yau, MD, of the University of Hong Kong, said in a statement.⁴ “Based on the cohort 6 findings, cabozantinib in combination with immunotherapy offers a potentially powerful and attractive new treatment approach that warrants further study in advanced liver cancer populations.”

REFERENCES


FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

Nivolumab Triplet Therapy in Advanced HCC Treatment

The triplet regimen of nivolumab (Opdivo), ipilimumab (Yervoy), and cabozantinib (Cabometyx) induced clinically meaningful responses in patients with advanced HCC who were treatment-naïve or resistant to or intolerant of sorafenib. The cohort data presented at the symposium is the first report of efficacy and safety of nivolumab and cabozantinib, with or without ipilimumab.

Combination treatment of atezolizumab (Tecentriq) plus bevacizumab (Avastin) led to significantly better patient-reported outcomes than treatment with sorafenib (Nexavar) in patients with unresectable hepatocellular carcinoma (HCC).³

CONFERENCE ROUND-UP GI CANCER
CONTINUING MEDICAL EDUCATION

Precision Medicine in Pediatric Oncology

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Describe the key principles and components of precision medicine in pediatric hematology-oncology
- Discuss the current approaches to molecular testing in the pediatric population and the genetic abnormalities that are known to be important in the setting of pediatric oncology
- Consider safety and efficacy data of ongoing trials using tropomyosin receptor kinase (TRK) inhibitors in pediatric oncology

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Precision medicine is an emerging approach for cancer treatment that has recently taken solid steps into clinical practice. The Precision Medicine Initiative has defined it as an emerging approach for the prevention and treatment of disease that considers individual variability in environment, lifestyle, and genes. Molecular diagnostics techniques that can analyze the individual genetic variability of tumors have provided greater understanding and additional strategies to treat cancers. For example, MYCN amplification in a patient with neuroblastoma is associated with a poor prognosis, so identification of this defect may indicate that treatment should be changed (as when standard chemotherapy and surgery are likely to be of no value). A predictive genetic defect provides information about the likelihood of the patient’s response to a specific treatment. For instance, an ALK mutation or amplification in a patient with neuroblastoma suggests the likelihood of response to an ALK inhibitor.

The use of next-generation sequencing (NGS) has greatly facilitated the understanding of pediatric cancer and identified additional therapeutic opportunities. These advances have been particularly striking in the assessment and treatment of pediatric cancers that have a different genetic makeup, with a fewer number of actionable targets, than adult tumors. The use of NGS has led to the increased use of targeted therapies and improved survival in children with leukemia and solid tumors. For example, the detection of somatic mutations, fusions, and other genomic abnormalities has resulted in the use of targeted therapies in Philadelphia (Ph) chromosome-positive and Ph-like acute lymphoblastic leukemia (ALL) and ALK-mutated neuroblastoma. Somatic genomic testing has become the standard of care in a variety of pediatric cancers. Genetic profiling has become particularly important in the evaluation of central nervous system (CNS) tumors, and the use of genetic profiling has been included in the World Health Organization classification of CNS malignancy.

In the section that follows, Theodore Laetsch, MD, discusses the current status of pediatric precision oncology and different clinical scenarios in which it can be effectively applied. He also discusses safety and efficacy data of targeted agents being used for the treatment of pediatric patients with oncological malignancies. The era of precision medicine is evolving to use not just molecular characterization of the tumor but actually a targeted agent to improve outcomes, and the same is now going on in leukemia, where they’re studying a variety of BCR-ABL-like leukemias, the Philadelphia-like leukemias, to see if a similar philosophy works with targeting of these fusions that are identified.

**Q:** What do you consider to be the key principles of precision medicine in the setting of pediatric hematology-oncology?

**DR LAETSC:** At the most basic level, precision medicine means refining the treatment based on the individual patient and tumor characteristics, and this has been going on for a long period of time using biomarkers to define therapy. I think some of the earliest examples of this are using the patient’s age or their white blood cell count when they initially presented to define the treatment for pediatric leukemia and pediatric ALL, but more recently, it has focused on the use of genetic markers.

**Q:** What is the current status of precision medicine in pediatric oncology in terms of clinical practice? How much variability is there between the different centers?

**DR LAETSC:** I think this is very cancer specific. For some cancers such as leukemia that I was just discussing, the approach is fairly standardized and is actually being studied in a large phase 3 study through the Children’s Oncology Group. But for other tumors, especially solid tumors, there are varying practices with different assays used at different centers, in different countries, and at different times in a patient’s disease course.

In particular, if you think about next-generation sequencing, there hasn’t been standardization to a particular assay with some centers using DNA-based assays, some using RNA-based assays, and some using a combination of these. I think it’s important as we think about this field moving forward, that we work to standardize these assays to make sure they all have the same sensitivity and specificity for the molecular alterations that are identified.

**Q:** When is molecular testing indicated? What should such testing involve?

**DR LAETSC:** The indication for molecular testing depends on the diagnosis and prognosis. As I’ve discussed, for some cancers, molecular testing is absolutely standard of care at the time of diagnosis, for example, in patients with neuroblastoma and leukemia. But for others, it’s more variable.

I’ve studied soft tissue sarcomas in particular, and we found that 80% of children with undifferentiated sarcoma either had a more specific diagnosis or a therapeutic target.
suggested by next-generation sequencing. We’re now studying this finding more broadly across patients with soft tissue sarcomas, and molecular testing is very important in these patients. I believe that next-generation sequencing should be indicated for all children with either difficult-to-define tumors when the diagnosis isn’t clear or for those whose tumor relapses or lacks a good standard-of-care treatment option. We try to identify these molecular biomarkers that may predict response to therapy.

**Q:** What do you consider to be the most clinically significant molecular genetic abnormalities in pediatric cancer?

**DR LAETSCH:** I’ve discussed a number of these potential molecular alterations, including MYCN amplification for neuroblastoma, and more recently, a discovery of ALK-activating mutations in neuroblastoma, which are now being targeted, as well as the Philadelphia chromosome and Philadelphia-like mutation in pediatric ALL.

More recently, however, there have been discoveries of more pan-cancer molecular alterations that are relevant across pediatric tumor types. These include the presence of microsatellite instability, and mismatched-repair–deficient tumors, for which pembrolizumab was recently granted FDA approval and the identification of fusions of the NTRK 1, 2, or 3 genes TRK fusions for which larotrectinib and entrectinib have recently been granted FDA approval.

**Q:** Could you describe the incidence and presentation of NTRK fusion-positive solid tumors and hematologic malignancies in pediatric patients?

**DR LAETSCH:** NTRK fusion-positive tumors are rare overall and are thought to occur in less than 1% of cancers. However, especially in pediatric oncology, there are diseases for which transfusions are pathognomonic, and these include infantile fibrosarcoma (the most common sarcoma in children younger than 1 year of age) and congenital megaloblastic lymphoma of the cellular subtype. In both of these illnesses, the diagnosis is essentially made by the identification of an NTRK fusion.

There are other cancers in which NTRK fusions are not pathognomonic but are occurring in greater than 5% of patients, and these include papillary thyroid cancer and melanoma. More recently, TRK fusions have been identified across the range of histologic subtypes of soft tissue sarcomas and high- and low-grade gliomas, as well as some other CNS tumors.

I think also, given the number of patients who have been sequenced and the variability of the techniques for sequencing, you can’t completely exclude the presence of NTRK fusions and other tumors. This has been seen in adult cancers when some very common types of cancer, such as lung cancer and colon cancer have NTRK fusions, but at very, very low frequencies. I don’t think we can exclude this finding in pediatric cancer.

**Q:** What is the evidence that TRK inhibitors are effective in treating these malignancies?

**DR LAETSCH:** Two TRK inhibitors have recently received FDA approval for the treatment of TRK fusion–positive cancers regardless of histology: larotrectinib and entrectinib. Larotrectinib demonstrated a 75% response rate across adults and children with a wide range of histologies harboring TRK fusions and was recently reported to have a 35-month median duration of response in those patients. In children, the results have been even more impressive with a response rate greater than 90% and a median duration of response not yet reached. Entrectinib demonstrated a 57% response rate in adults with TRK fusion–positive malignancy, with a 10-month median duration of response.

**Q:** What is the safety profile of the TRK inhibitors?

**DR LAETSCH:** The TRK inhibitors are generally well tolerated. A pediatric phase 1-2 study of entrectinib is ongoing, but the preliminary results reported at ASCO in 2019 demonstrated a response in a high proportion of children with fusions of NTRK, ALK, or ROS1, as entrectinib targets all 3 of these genes. Both agents have also been shown to have activity in patients with CNS tumors.

I think it’s important to note when describing these results that these are nonrandomized studies, so cross-study comparisons are not possible with the data, and additional long-term data will be needed to evaluate the efficacy and safety of both of these drugs.

There’s also ongoing pediatric studies of next-generation TRK inhibitors, which may overcome some of the resistance that develops in the first-generation drugs. These include selircteinib (LOXO-195) as well as repotrectinib.
Larotrectinib has shown some on-target neurologic toxicity, including fatigue and dizziness, some gastrointestinal side effects, including hepatotoxicity elevations in liver function tests, and typically mild cytopenias. Entrectinib has also shown CNS toxicity, including vision disorders and has warnings for the presence of congestive heart failure, skeletal fractures, hepatotoxicity, hyperuricemia and QT prolongation, and both agents have a risk for fetal toxicity. It’s also important to note that each of these agents has only recently been developed, so long-term toxicity in developing children remains unknown with both drugs.

Q: What are the ongoing trials regarding TRK inhibitors that a pediatric hematologist-oncologist should be aware of?

DR LAETSCH: There are several ongoing clinical trials. These include a frontline study testing larotrectinib for children with newly diagnosed TRK fusion–positive solid tumors that I lead through the Children’s Oncology Group and the pediatric match, which is an NCI Children’s Oncology Group study evaluating larotrectinib for children with TRK fusion–positive tumors that relapse. As I mentioned earlier, there are ongoing studies of at least 2 next-generation TRK inhibitors that are evaluating the ability of these drugs to treat patients who may develop resistance to the first-generation drugs. There are also industry-sponsored long-term follow-up studies evaluating the safety of larotrectinib in children, to find additional long-term safety data.

Q: What advice can you offer to pediatric hematologist-oncologists in the community about the use of TRK inhibitors?

DR LAETSCH: I think there are now multiple TRK inhibitors FDA approved for the treatment of children. It’s notable that entrectinib is approved for patients 12 and older and the pediatric phase 1 study is ongoing. Larotrectinib is approved for children of any age, and there is a liquid formulation available that enables dosing of young children in whom these TRK fusions are common. I think that it’s important to think through the timing of testing of these patients because without identification, patients won’t have access to these drugs. At the time of relapse or progression, this is especially important. It is also important in patients with high-frequency tumors at initial diagnosis to identify whether they may be candidates for either of these ongoing clinical trials or commercial use of 1 of these agents.

Q: What role do you think targeted therapies will have in pediatric oncology in the future?

DR LAETSCH: The use of targeted therapy in pediatric oncology is increasing very rapidly. I think there’s still a large portion of patients for whom we can’t identify an effective targeted therapy. There are, however, a number of ongoing clinical trials of both TRK inhibitors that we’ve discussed and also other drugs targeting other particular kinases that are activated in pediatric cancer. These are in phase 3 clinical trials or are currently in commercial use. So, I think this is a field that will continue to grow as we gain additional understanding about the genomics of pediatric cancer and which tumors are targetable.

FIVE KEY REFERENCES

For full reference list, visit cancernetwork.com/PediatricPrecisionMedicine
Urology Times
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All human cells maintain a redox balance between reactive oxygen species (ROS) and antioxidants, such as NQO1, to resist oxidative stress. The optimal redox balance differs between cells and determines their specific “redox signature,” which can have downstream effects on potent oncogenic signaling pathways, including STAT3.

Research suggests that a subset of cancer cells, including some cancer stem cells, possess a distinct redox signature that may make them susceptible to approaches that generate cytotoxic levels of ROS. These cells signal to other cells in the tumor microenvironment and promote the phosphorylation of STAT3. The presence of phosphorylated STAT3 in a tumor may indicate this redox signature and favorability to ROS-generating intervention.

Learn more about ROS generation in cancer cells at www.bostonbiomedical.com