Lung Cancer
HEATHER WAKELEE, MD, on
Evaluating the Role of Targeted Therapy in Lung Cancer
‘This will have an impact to change cure rates’

Breast Cancer
Controversies and Disparities in Breast Reconstruction
Tran B. Ho, DO; William C. Wood, MD; and Preeti D. Subhedar, MD, MSPT

GI Cancer
Focus on Pancreatic Neuroendocrine Tumors
Ana Maria Cristina De Jesus-Acosta, MD

Hematologic Malignancies
Recognizing Hypercalcemia in CLL/SLL
Mehmet Sitki Copur, MD, FACP; Whitney Wedel, MD; Pornchai Jonglertham, MD; Carlene Springer, APRN; Adam Horn, MD

GU Cancer
Novel Combination in Metastatic RCC
Kristie L. Kahl

Immunotherapy
The Future of CAR T-Cell Therapy
Hannah Slater
**INDICATION**

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Ischemic Cardiovascular Events** — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

**Fractures** — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

**Rash** — In a randomized study (SPARTAN), rash occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Rashes were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

**Seizure** — In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

**Embryo-Fetal Toxicity** — The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise females with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA®[See Use in Specific Populations (8.1, 8.2)].

**ADVERSE REACTIONS**

**Adverse Reactions** — The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (2% or over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, anemia, rash, decreased appetite, fall, weight decreased, hyperthyroidism, hot flush, diarrhea, and fracture.

**Laboratory Abnormalities—All Grades (Grade 3-4)**

- **Hematology** — In the TITAN study, while blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the spartan study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%). Leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.6%). Lymphopenia ERLEADA® 41% (2%), placebo 21% (2%).
- **Chemistry** — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (0%), placebo 12% (0%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%). Hyperuricemia ERLEADA® 78% (0%), placebo 59% (0%). Hyperglycemia ERLEADA® 67% (0%), placebo 60% (0.8%). Hyperkalemia ERLEADA® 32% (0%), placebo 22% (0.5%).
- **Rash** — In 2 randomized studies, rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs. 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 7 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

**Hypothyroidism** — In 2 randomized studies, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo. Median TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

**DRUG INTERACTIONS**

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP3A4 or P-gp inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [See Dose and Administration (2.3)].

Effect of ERLEADA® on Other Drugs — ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2B6 in humans. Concomitant use of ERLEADA® with medications that are substrates of UGT (uridine diphosphate glucuronosyltransferase) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

P-gp, BCRP, or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp) and organic anion transporting polypeptide 1B1 (OATP1B1) (see Drug Interactions). Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued. Please see Brief Summary of full Prescribing Information for ERLEADA® on subsequent pages.

**NEW INDICATION**

Now approved for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).

**ERLEADA® + ADT reduced the risk of death by 33% vs placebo + ADT**

(Median overall survival was not estimable in either arm; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053)

**Visit erleadahcp.com**
ERLEADA® (apalutamide) tablets

Eight patients (1%) who were treated with ERLEADA died from adverse reactions. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral hemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse reaction of cardiopulmonary arrest (n=1). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematoma. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (3%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

### Table 3: Adverse Reactions in SPARTAN (mmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Laboratory Abnormality</th>
<th>ERLEADA (n=803)</th>
<th>Placebo (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Fatigue⁴</td>
<td>39</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Muscle–skeletal and connective tissue disorders</td>
<td>16</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>25</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>12</td>
<td>0.1</td>
<td>9</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>11</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>25</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>18</td>
<td>0</td>
<td>16</td>
</tr>
</tbody>
</table>

### Table 4: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5 All Grades) in SPARTAN (mmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA (n=803)</th>
<th>Placebo (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41</td>
<td>2</td>
</tr>
</tbody>
</table>

¹ Does not reflect fasting values

**Drug Interactions**

**Effect of Other Drugs on ERLEADA**

Strong CYP2C9 or CYP3A4 inhibitors

Co-administration of a strong CYP2C9 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability (see Dosage and Administration (2.2) in full Prescribing Information). Mild or moderate inhibitors of CYP2C9 or CYP3A4 are not expected to affect the exposure of apalutamide.

**Effect of ERLEADA on Other Drugs**

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP2C9, CYP2C19, or CYP3A4, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UGT glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity (see Clinical Pharmacology (12.3) in full Prescribing Information).

P-gp, BCRP or DABT1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/DABT1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or DABT1B1 can result in lower exposure to these medications. Use caution if substrates of P-gp, BCRP or DABT1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued (see Clinical Pharmacology (12.3) in full Prescribing Information).

**Use in Specific Populations**

**Pregnancy**

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy (see Clinical Pharmacology (12.1) in full Prescribing Information). There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo–fetal developmental toxicology studies were not conducted with apalutamide.

**Lactation**

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

---

1. Includes fatigue and asthenia
2. Includes rash, macular–papular, rash generalized, urticaria, rash puritic, rash macular, conjunctivitis, erythema multiforme, rash palpable, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mucocutaneous, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
4. Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
5. Includes appetite disorder, decreased appetite, early satiety, and hypophagia
6. Includes peripheral edema, generalized edema, edema, edema genital, panicle edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

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**Use in Specific Populations**

**Pregnancy**

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy (see Clinical Pharmacology (12.1) in full Prescribing Information). There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo–fetal developmental toxicology studies were not conducted with apalutamide.

**Lactation**

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.
Brief Summary of Prescribing Information for ERLEADA® (apalutamide)

ERLEADA® (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE
ERLEADA is indicated for the treatment of patients with:
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Ischemic Cardiovascular Events
Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within six months of randomization were excluded from the SPARTAN and TITAN studies.

Fractures
Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 374 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls
Falls occurred in patients receiving ERLEADA with increased frequency in the elderly [See Use in Specific Populations]. Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

Seizure
Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA.

Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (≥1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse reaction</th>
<th>ERLEADA N=524</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue1,2</td>
<td>26</td>
<td>3</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Muscle/skeletal and connective tissue disorders</td>
<td>Arthropalgia3</td>
<td>17</td>
<td>0.4</td>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash2</td>
<td>28</td>
<td>6</td>
<td>9</td>
<td>0.6</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flush</td>
<td>23</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>18</td>
<td>8</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia
2 Includes rash, maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
3 Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (9% versus 6% on placebo), muscle spasm (3% versus 2% on placebo), dysgeusia (3% versus 1% on placebo), and hypothyroidism (4% versus 1% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Differences ≥ 5% All Grades) in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
<td>19</td>
<td>0.6</td>
</tr>
<tr>
<td>Chemistry</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hypertiglyceridemia1</td>
<td>17</td>
<td>3</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Does not reflect fasting values

Non-metastatic Castration-Resistant Prostate Cancer (nmCRPC)
SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone ( GnRH) analog or had prior bilateral orchietomy. The median duration of exposure was 20.3 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

The most common adverse reactions (≥ 10%) that occurred more frequently in the ERLEADA-treated patients (≥ 1% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypotension, hot flush, diarrhea, and fracture.

ERLEADA® (apalutamide) tablets
ERLEADA® (apalutamide) tablets

Females and Males of Reproductive Potential

Contraception

Males
Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. [see Use in Specific Populations].

Infertility

Males
Based on animal studies, ERLEADA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) in full Prescribing Information].

Pediatric Use

Safety and effectiveness of ERLEADA in pediatric patients have not been established.

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over.

No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 38% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Ischemic Cardiovascular Events

• Inform patients that ERLEADA has been associated with ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur [see Warnings and Precautions].

Falls and Fractures

• Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see Warnings and Precautions].

Seizures

• Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure [see Warnings and Precautions].

Rash

• Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash [see Adverse Reactions].

Dosage and Administration

• Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.

• Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.

• Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1) in full Prescribing Information].

Embryo-Fetal Toxicity

• Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman [see Warnings and Precautions].

Infertility

• Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA [see Use in Specific Populations].

Manufactured by: Manufactured for:
Janssen Ortho LLC Janssen Products, LP
Gurabo, PR 00778 Horsham, PA 19044

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cp-50509v2
LUNG CANCER: Cover
Evaluating the Role of Targeted Therapy in Lung Cancer
Heather Wakelee, MD
ONCOLOGY recently sat down with Heather Wakelee, MD, ahead of the 17th Annual Winter Lung Cancer Conference to discuss major trends in lung cancer.

CANCER SURVIVORSHIP: Continuing Medical Education
Reassessing Cancer Survivorship in the Era of Personalized Medicine
Don S. Dizon, MD

HEMATOLOGIC MALIGNANCIES: Clinical Quandaries
Hypercalcemia in a Patient with Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia
Mehmet Sitki Copur, MD, FACP; Whitney Wedel, MD; Pornchai Jonglertham, MD; Carlene Springer, APRN; and Adam Horn, MD
Mary Lanning Healthcare professionals review a case of a 64-year old man diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma who presented with symptomatic hypercalcemia.
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The editorial content of this issue is designed to provide practitioners with the latest developments and treatments in the field of oncology. The articles cover a range of topics, from understanding lung cancer treatment advances to the molecular characterization and treatment of pancreatic neuroendocrine tumors.

The editors are pleased to announce the availability of our new parent company’s continuing education activities. We’ve picked this one especially for our Oncology readers. Go to: https://bit.ly/2IRAnkZ

Go to: https://bit.ly/2IRAnkZ
ONCOLOGY and its website, CancerNetwork.com, provide oncologists with the practical, timely, clinical information they need to deliver the highest level of care to their patients. Expert authors and peer review ensure the quality of ONCOLOGY and CancerNetwork.com’s articles and features. Focused discussions capture key clinical take-aways for application in today’s time-constrained practice environment.
CHAIRMAN’S LETTER

Understanding Lung Cancer Treatment Advances

Dear Reader,

As the treatment landscape for lung cancer continues to evolve, especially within subgroups of patients with particular mutations and molecular profiles, it can be difficult for oncologists to stay up-to-date.

However, meetings like the 17th Annual Winter Lung Cancer Conference can help to bring healthcare providers in this space together. In this issue of ONCOLOGY, we spoke with Heather Wakelee, MD, an associate professor of medicine (oncology) at Stanford University Medical Center and the meeting’s co-chair, about the major advances in lung cancer.

With such advances, Wakelee notes how this can affect patient-physician communication when it comes to making treatment decisions. “It is [about] making sure that we do not act too quickly and it [has] to be a partnership with the patient. A new diagnosis of cancer is scary,” she says, adding that patients usually want to start treatment immediately, but sometimes time is needed. “Part of our job as oncologists is being able to have [effective] communication. [We need] to help [patients] understand why we [may] need a little bit longer...as opposed to...feeding into the anxiety and...starting the first [treatment we] could [begin].”

Moreover, such communication is also key for all healthcare providers to be discussing the risks associated with the growing vaping trend. While many turn to vaping as a way to quit smoking cigarettes, more never-smoking adolescents and young adults are also joining in on the action. While the exact effects of vaping are still unknown, Wakelee urges for smoking cessation programs to be incorporated into screening recommendations.

Also in this issue, Mehmet Sitki Copur, MD, FACP; Whitney Wedel, MD; Pornchai Jonglertham, MD; Carlene Springer, APRN; and Adam Horn, MD, address the case of hypercalcemia in a 64-year-old man with small lymphocytic lymphoma/chronic lymphocytic leukemia. Moreover, hear from Ana Maria Cristina De Jesus-Acosta, MD, an assistant professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Medicine, about the molecular characterization and treatment of pancreatic neuroendocrine tumors.

Within these pages, you will also find highlights from the International Kidney Cancer Symposium as well as the 61st American Society of Hematology Annual Meeting & Exposition.

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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ONCOLOGY recently sat down with Heather Wakelee, MD, ahead of the 17th Annual Winter Lung Cancer Conference being held February 7-9, 2020, where she will serve as a co-chair for the meeting. Wakelee, an associate professor of medicine (oncology) at Stanford University Medical Center, discussed major trends in lung cancer, such as treatment advances, updates in genetic testing, the unknown risks of vaping, and where the field is headed next. She also described why it is important for oncologists to attend the program led by world-class thoracic oncologists.

Treatment Advances

Q: How would you characterize the major trends in lung cancer treatment research right now? Is there an overarching theme you see in clinical development, particularly a theme that is going to be reflected in the lung cancer conference?

DR. WAKELEE: When we think about lung cancer, we have to think about it in different phases: prevention and early detection, early stage, improving cure rates in early stages, and then we have to think about metastatic disease.

Prevention and early detection, there’s obviously a lot happening now around vaping. And most of that, of course, focuses on these acute illnesses. But there is a growing, albeit still small, body of literature about the links to cancer. I do not think any of us that work in the healthcare field are in any way surprised that there is going to be a cancer link; it is something that has been suppressed thus far by the companies involved. But that is definitely something where there is going to be more research coming out.

For early detection, there is a lot of screening with scans, but also a lot of what is being done with circulating tumor DNA and other nonradiographic techniques for early detection. When we think about earlier stages of disease, targeted therapies are being discovered and looked at there, although we do not have any definite proof. With the immune therapies, there is even more excitement, and we have definite proof of principle with the PACIFIC trial. In that study, patients with stage III disease received durvalumab (Imfinzi), a checkpoint inhibitor, after chemotherapy radiation and clearly showed an improvement in cure.

Now there is a lot of trials with immune checkpoint in-
We have known about mutations in their tumors. Patients are those with targets- is focused. Is where a lot of the research and stopped working. That patient or when it worked therapy does not work for a really trying to do is figure out what to do when those drugs stop working. So, there are many ongoing trials looking at various combinations of other immune-altering drugs that are not the standard programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) checkpoint inhibitors. There was just some data out with the cytotoxic T-lymphocyte-associated protein 4 and PD-1 checkpoint inhibitors, ipilimumab (Yervoy)/nivolumab (Opdivo), respectively, that were very encouraging. But what we are really trying to do is figure out what to do when an immune therapy does not work for a patient or when it worked and stopped working. That is where a lot of the research is focused.

A separate group of patients are those with targetable mutations in their tumors. We have known about EGFR, ALK, ROS1, but now there are more and more data coming out in some of the less common types such as HER2, RET, and NTRK. There are also some data with 1 of the subtypes of KRAS. So, those molecularly targeted treatments are still rapidly evolving as well.

**Q:** What targeted therapies have recently been approved? What results are you most eagerly anticipating?

**DR. WAKELEE:** Every few months it seems that we are hearing about new targeted agents. The one that everyone is talking about right now is AMG 510, and there’s also a similar compound made by Mirati. These agents are targeting 1 particular subset of KRAS, which is a big target because it is responsible for a huge percentage of adenocarcinoma, and was previously thought to be fairly resistant to therapy. There are multiple, different KRAS mutations, and this one that is being investigated is the KRAS G12C mutation, and the C part of that is important. It is very limited to that one particular subset, but it’s a fairly big subset of a very big subset of lung cancer. So, that is very exciting. We still are only seeing data from dozens of patients as opposed to hundreds of patients, and it is not clear when we are going to get FDA approval. However, because it is the first step in that direction, it is likely going to be relatively soon. We will have to see. And, it is not something that works for all KRAS mutations. It works for KRAS lung cancer, but it does not look like it is working for KRAS-positive colon cancer. I haven’t seen any data with KRAS-positive melanoma. That is why there is a lot of excitement around it, because so many different diseases can be impacted.

**Q:** How do you decide who gets immunotherapy with chemotherapy and who does not?

**DR. WAKELEE:** Right now, it is still based on the PD-L1 level, and so if someone has a very high PD-L1 level, we will go ahead and give single-agent pembrolizumab (Keytruda). If they don’t have a very high PD-L1 level, we usually give pembrolizumab in combination with chemotherapy. If, on the other hand, someone has an EGFR, ALK, ROS1, or RET mutation, or many of these other driver mutations, we know that even if they have high PD-L1 expression, they are still not likely to respond to a checkpoint inhibitor, and so we ignore PD-L1 expression. For patients who do not have a driver mutation, we look at PD-L1 expression. If it is high, if the patient is not very symptomatic from their disease, we are comfortable giving single-agent immunotherapy. If they are symptomatic, then we would consider giving pembrolizumab with chemotherapy because the response rates are higher.

Now it gets more complicated because we just saw the IMpower110 trial data at the European Society for Medical Oncology Congress and atezolizumab (Tecentriq) was also active as a single agent compared with chemotherapy when PD-L1 expression was high. They used a slightly different test, however. Also, a nivolumab/ipilimumab combination showed activity regardless of PD-L1 expression or tumor mutation burden. But, it still was not active in everybody, and there is some question about how we select out the patients who might be best served with that combination as opposed to chemotherapy or other combination regimens.

**Genetic/Genomic Testing**

**Q:** When can providers use a general diagnostic to decide on...
PD-L1 is produced by tumors to suppress the immune system. Blockers of the PD-L1 and PD-1 interaction are an important new anticancer drug class to treat lung cancer.

**a patient’s treatment course?**

**DR. WAKELEE:** Well, we always need to make sure that appropriate testing has been done to understand the molecular basis of the tumor, especially for someone with metastatic disease. It is not enough to just know PD-L1 expression. You have got to know the standard driver mutations. Then, you have enough information to make that first-line treatment choice, and that is going to be standard driver mutation drugs, chemotherapy, or chemotherapy plus immune therapy. That can be sorted out (if it is one of the standards) by almost any oncologist who manages lung cancer. But, when we get into the rare subtypes, patients really need to talk to someone who is a lung cancer specialist. And, it is important at the time of progression. That is where there is a lot of variations that can occur, and that is where the specialist can usually provide some good insight.

**Vaping**

**Q:** What do we know about vaping and its unknown risks?

**DR. WAKELEE:** There are some data supporting that vaping is somewhat less toxic than smoking cigarettes. Also, there are some data for people who were smoking cigarettes and are able to switch from smoking cigarettes to vaping. Less data exists for how many of those patients can go from vaping to not having any tobacco consumption or any nicotine consumption. What we worry about more is that there is clearly an epidemic of more young people taking up vaping who would not have otherwise taken up any sort of a nicotine habit. It might be less harmful than a cigarette but it is not harmless.

We as a healthcare community are facing the challenge that the marketing of e-cigarettes has been so powerful that it messages that e-cigarettes can help people quit smoking. They have done a lot of opinion polls in young people and otherwise healthy people, where people have the sense, “Oh yes, it’s harmless,” which is exactly what the tobacco industry was trying to get us to believe. Now there are some data coming out in animal models that suggest there is a clear linkage between vaping and cancer. In a mouse model study that mimicked vaping, mice vaping with tobacco were developing lung cancer compared with those vaping without nicotine.
Q: Is elevated cancer risk something that is inherent to nicotine?

DR. WAKELEE: That is a little bit less clear, but I think if you are doing anything that is going to damage the lungs—any heated products inhaled into the lungs is going to damage the lungs, right? Over time, inherently it makes sense that it is going to cause a malignancy in addition to the upfront toxicities.

Q: Most lung cancers are diagnosed late because it takes a while for symptoms to develop. How do most lung cancers get diagnosed? How might we be able to change that so we catch more of them earlier while they are still curable?

DR. WAKELEE: We know from multiple trials that you can reduce mortality from lung cancer if you have early detection with annual computed tomography (CT) scans. We can change the mortality of the malignancy because we are finding it early and curing patients. Despite that very clear mortality benefit, in the United States, only 4% of people who would be eligible for scans actually get screened.

Q: Why is that? Are doctors not saying, “Hey, you should be getting a lung cancer screening?” Are people declining it or are insurers not paying for the CT scan?

DR. WAKELEE: All of the above. Some private insurers are not paying, even though screening is in all the standard guidelines now. A lot of primary care physicians are not emphasizing it. Also, patients are not always agreeing to do it or some who do use it as a justification to continue smoking if they get a clean scan. What really needs to be happening is getting primary care physicians more aware of this, that CT scans provide even better mortality reduction than some of the standard screenings that we recommend. Smoking cessation needs to be part of that screening.

Q: Why is it important to attend?

DR. WAKELEE: We have a really great panel of folks from around the country, putting perspective on most of these hot topics. With immune therapy, we have a whole session focusing on these questions of who should get it and when. For example, should you ever stop it? Because that is really an area we do not understand. We have several people talking about a lot of the different targeted drugs, and really focusing on those newer agents. Also, we are discussing what we should be thinking about with testing and, when we find these mutations, how do we weigh out options with all of the different agents coming forward? There are new approvals every year, several of them.

Q: Do you have a sense of how the role of focus of the meeting has changed over the years?

DR. WAKELEE: We have always strived to look at what is happening in lung cancer across different stages of disease, with all of the newest developments over the years. We have always tried to bring in dynamic faculty from around the country. With Miami Lung Cancer Congress, we have also tried to have some speakers who are a little bit early in their career, maybe not as well known, but are dynamic speakers that give the audience a different perspective from what they hear at other conferences.

“PD-L1 is produced by tumors to suppress the immune system. Blockers of the PD-L1 and PD-1 interaction are an important new anticancer drug class to treat lung cancer.”

- Heather Wakelee, MD

Key Question

What sort of genetic testing should patients with lung cancer and/or their tumors be undergoing right now?

DR. WAKELEE: Anybody diagnosed with adenocarcinoma absolutely should get what we call next-generation sequencing. I personally believe that we should be looking at the top 15 genes (minimum) where we actually have drugs. Even if they are still participating in clinical trial, most patients are going to be able to get access, and so those are mutations like RET, NTRK, ROS1, EGFR, ALK, BRAF, and HER2. If one of those mutations is found with earlier sequencing, like EGFR mutations, going beyond that is not that critical. But, I still get patients coming to see me who are young and have never smoked and they are telling me, “Oh, well, I don’t have a driver mutation,” and then you look and the only things that have been assessed are EGFR and ALK mutations. That is not okay. There are also a lot of companies out there claiming that they are doing next-generation sequencing, but it is not really the full panel. For example, we can drastically alter the outcomes in patients with MET exon 14 or RET mutations if we find them.
Q: What is your advice for other oncologists?

DR. WAKELEE: Go to these conferences. I think it is really hard to stay up to date otherwise. It is very easy to get lost in everything new that comes out constantly.

Looking Forward

Q: What is your major investigative focus right now?

DR. WAKELEE: I am doing some adjuvant work, so giving immune therapy after surgery, and a lot of the trials are completing enrollment, so we should be getting data at some point. I am also involved in some neoadjuvant therapies, the treatments before surgery, and I think both of those approaches look very promising.

We are doing a lot of translational work with circulating tumor DNA with my colleague Maximilian Diehn, MD, PhD, and Arash Ash Alizadeh, MD, PhD. I am very excited about the potential for that technology to alter the adjuvant setting—who gets treatment and who does not after surgery by being able to figure out what patients are at high risk of treatment resistance over time. I think that is a really exciting area. Also, there is technology being looked at for earlier detection, although it is not at the forefront of research right now.

In the metastatic setting, we are doing a lot of different work on what immune combinations are going to be able to overcome resistance. Also, we are looking at resistance pathways, especially in the setting of EGFR mutations. That is where we have always had the greatest focus. It is because we have a very large number of patients with EGFR-mutant lung cancer. I am also doing some population science work, really trying to get at the etiology of why young people who have never smoked are getting lung cancer and often have EGFR-mutant disease.

Q: Are we seeing fewer people getting lung cancer because of decreased smoking rates?

DR. WAKELEE: We are definitely seeing lower rates of lung cancer. If you look at lung cancer mortality across the country, there is a clear reduction, especially in men. You can track when smoking started to decrease and when lung cancer mortality started to decrease, and those curves absolutely parallel with each other. It just shifted out by approximately 10 years. These are some of the strongest data for the smoking link. Women have not stopped smoking, but there have always been fewer women smoking versus men. When all the smoking health risk data came out in the 1960s and 1970s, men stopped smoking more than women. Women actually started smoking more. There was a lot going on at that time, so we are just now seeing that, at least in the United States, smoking rates in women are decreasing.

Q: Looking back at the past year, what big study results have come out in terms of changing practice?

“What we worry about more is that there is clearly an epidemic of more young people taking up vaping who would not have otherwise taken up any sort of a nicotine habit.”

-Heather Wakelee, MD

Q: Are there areas of lung cancer you feel need more emphasis?

DR. WAKELEE: The biggest radical changes would go back a year and a half with the use of first-line chemotherapy plus immune therapy, and then the PACIFIC study—giving immune therapy after chemoradiation. Those are the most practice-changing developments. A lot of the other more recent updates have been newer targeted drugs, like the newer ROS1 agents and RET therapies. These are very exciting, but are not all available yet, and again, are useful in pretty small subsets of patients. It is not a paradigm shift because we know that if we find the right target and we find the right drug for the target, it is going to be better than chemotherapy or immune therapy, but it is still interesting.

Q: Looking forward, which study results are you most eager to see?

DR. WAKELEE: Right now it is the early-stage trials trying to evaluate adjuvant versus neoadjuvant, so post-versus pre-surgery, and immune therapy because that is going to have an impact to change cure rates for a lot of people. Also, there are dozens of trials assessing what to do when immune therapy stops working. How do we get that to work better? What can we tweak in the immune system to work better as opposed to offering single-agent checkpoint inhibitors? I do not know which of these is going to be the winner because there are so many of them, and the early signals have not necessarily been hitting the ball out of the park.

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Findings from a planned interim analysis of the Ib/II Study 111 showed that lenvatinib (Lenvima) plus pembrolizumab (Keytruda) induced a disease control rate of 94% in patients with metastatic clear cell renal cell carcinoma (RCC) who regressed following treatment with a programmed cell death protein 1/programmed cell death-ligand 1 inhibitor.

“These are very dramatic results,” study author Chung-Han Lee, MD, PhD, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York City, said in an interview with CancerNetwork® ahead of the International Kidney Cancer Symposium, held November 15-16, in Miami. “It’s the first data…looking at any of the (tyrosine kinase inhibitor [TKI]/immunotherapy) combinations after people have already progressed on a checkpoint inhibitor. It’s essentially the only data that we have for this type of combination in this space.”

The open-label study was originally designed as a phase Ib/II study for patients across multiple tumor types who had one or more prior lines of therapy with a checkpoint inhibitor, and involves up to 360 participants, including 33 patients in the metastatic clear cell RCC subgroup. Lee said the trial is still recruiting patients and hopes to eventually accrue a population of 100. Patients were assigned to 20 mg daily lenvatinib plus 200 mg intravenous pembrolizumab every 3 weeks until progression or toxicity.

The objective response rate (ORR) at week 24, the primary end point, was 61% (95% CI, 42%-77%). The confirmed ORR by investigator review was 64% (95% CI, 45%-80%) and was made up of all partial responses. An additional 10 patients (30%) had stable disease and 2 (6%) were not evaluable for response. The duration of response was 9.1 months (95% CI, 6.1-not evaluable). The median time to response in responders was 1.6 months (95% CI, 1.1-14.0). Progression-free survival was 11.3 months (95% CI, 7.3–not evaluable) using the immune-related Response Evaluation Criteria in Solid Tumors.

Lee stated that the safety results were “fairly characteristic” of patients treated with a VEGF/immune checkpoint inhibitor combination. Eighteen of the 33 patients had grade 3 or 4 adverse events, the most common being diarrhea, fatigue, and dysphoria. Six patients (18%) experienced any-grade hypothyroidism and 2 each (6%) experienced colitis, hyperthyroidism, or a severe skin reaction. One patient developed pneumonitis.

The results show that there are options even after a single immune checkpoint inhibitor has been exhausted, said Lee. “I think it becomes a really important question, because right now in the first-line setting a lot of people are either being treated with dual checkpoint inhibitors such as (ipilimumab [Yervoy]/nivolumab [Opdivo]) or are being treated with some TKI/immunotherapy combination,” Lee said.

“What the protocol and the results of the clinical trial that we did really shows is that, in this space, we can still get quite impressive responses to a combination like lenvatinib plus pembrolizumab,” he added. “It really is promising—it really is the first prospective data that we have for this kind of combination in this setting—and it certainly is very exciting, and the adverse events are manageable.”

The trial will continue into 2020. Although it is still too early to determine overall survival, the combination is also being tested as a first-line treatment in a phase III trial, Lee said. “I think we’re very excited to see what the final results will end up being,” he added.

**KEY REFERENCE**

Breast Reconstruction in the Setting of Postmastectomy Radiotherapy: Controversies and Disparities

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ABSTRACT: The complex decision of breast reconstruction in the setting of postmastectomy radiotherapy (PMRT) involves an understanding of the indications of PMRT and weighing the risks and benefits of various reconstruction options suitable for each patient. Classic indications for PMRT include patients with at least T3 tumors, 4 or more positive lymph nodes, and/or positive surgical margins. The benefit of PMRT in patients with T1-T2 tumors with 1 to 3 positive lymph nodes, however, remains unclear. Breast reconstruction is known to improve quality of life in breast cancer patients. Reconstruction rates have continued to increase despite the lack of medical consensus in these patients with early cancers and limited nodal burden. A collaborative effort among providers is therefore of utmost importance in selecting an optimal approach of reconstruction in the setting of PMRT to minimize postoperative complications. In this review, we discuss the advantages and disadvantages of each reconstruction method with PMRT and highlight the practice patterns at different types of institutions, especially noting the disparities seen at safety net institutions. By refocusing on this important topic, we hope to encourage a multidisciplinary effort to reduce disparities and find innovative algorithms that can be applied to patients at diverse institutions.
as well as the paucity of data applicable to diverse institutions. In doing so, we hope to draw further attention and investigation into developing algorithms that help providers improve outcomes for these patients.

**Implant-based breast reconstruction and radiotherapy: advantages and disadvantages**

Implant-based breast reconstruction represents 80% of the reconstruction performed after a mastectomy.[9,10] The implant can be composed of saline or silicone. Anatomically, it can be placed in the subpectoral space, under the pectoralis muscle, or prepectoral space, above the pectoralis muscle. Implant-based breast reconstruction can be performed in conjunction with a mastectomy as an immediate, one-stage, direct-to-implant procedure, or in a delayed fashion as a separate procedure several months after both the mastectomy and radiation have been completed.

A delayed-immediate reconstruction is a two-stage procedure in which a tissue expander is first placed during the mastectomy. The timing varies with regard to when a tissue expander is inflated relative to when radiation is delivered. Radiation can precede or be delivered after placement of the tissue expander. The tissue expander may be fully inflated during surgery or undergo rapid inflation in the weeks following surgery. In either of these cases, the second stage occurs after PMRT is completed and the tissue expander is then exchanged for a permanent implant.

There are some advantages to a direct-to-implant procedure, particularly in the short-term period as well as if the patient does not require PMRT. The first advantage is the immediate creation of a breast mound that lends itself to an immediate psychosocial benefit.[6,8] Also, it is well-tolerated and can mostly be completed in a single procedure, which reduces the overall operative and anesthesia time as well as duration of hospital stay.[8] Although there is an operative advantage to a one-stage procedure, patients who receive immediate implant reconstruction are at risk for long-term complications, especially in the setting of PMRT. These patients have a higher incidence of capsular contracture and return to surgery for subsequent revisions compared to patients who receive autologous reconstruction or tissue expander placement.[6,11,12]

Although delayed-immediate reconstruction is a two-stage procedure, it allows for revisions that may arise after the completion of radiation, such as capsulotomy and other procedures for symmetry. [6] A review of several studies examining immediate and delayed-immediate implant reconstruction found that risks of capsular contracture, infection, or implant exposure could be as high as 37% in patients who received PMRT compared to those who did not receive it.[6] Although multiple office visits may be required for tissue expansion, delayed-immediate reconstruction affords patients a choice between either a permanent implant or an opportunity for autologous reconstruction during the second-stage procedure.[6,8]

**Autologous breast reconstruction and radiotherapy: advantages and disadvantages**

Autologous breast reconstruction involves using a tissue flap that is transplanted from another site in the patient’s body to reconstruct the breast. The transplanted tissue can be rotated into the breast by maintaining its original blood supply as a pedicled flap or it can be transplanted as a free flap with the blood vessels being distantly anastomosed with those in the breast.[8] Different flaps include the transverse rectus abdominis myocutaneous (TRAM) flap, deep inferior epigastric perforator (DIEP) flap, latissimus dorsi flap, transverse upper gracilis (TUG) or thigh flaps, or gluteal flaps. Similar to implant-based reconstruction, autologous reconstruction can be performed in an immediate or delayed fashion. A breast implant can also be placed along with an autologous flap if the volume provided by the flap alone is inadequate.

Autologous reconstruction can be advantageous due to its natural cosmetic outcome as the tissue settles over time, and it can be used in patients who do not desire implants.[8] The time needed for tissue harvesting and microvascular anastomoses leads to a longer operation and recovery time compared to implant-based reconstruction, eliminating this option in patients who are poor surgical candidates. Autologous reconstruction in the setting of PMRT can lead to fat necrosis, contracture, and wound issues, although the incidence of these complications may be higher in immediate versus delayed autologous breast reconstruction.[6,8,13]

The 2018 National Comprehensive Cancer Network guidelines recommend autologous reconstruction as the preferred reconstruction option in patients undergoing PMRT.[14]

**Controversies and disparities**

Data on the preferred method and timing of reconstruction with adjuvant radiation have been conflicting. A literature review showed less postoperative complications, failure, and morbidity in patients receiving radiation with autologous reconstruction versus implant-based reconstruction.[6] A meta-analysis found a similar trend of reconstructive complications and failures in patients receiving immediate implant reconstruction and PMRT.[15] When comparing immediate to delayed-immediate implant-based reconstruction, a prospective multicenter study revealed similar complication rates in patients receiving radiation with a tissue expander versus those with an implant.[16]

Reported complications vary depending on the location of the implant as well. Several early studies have compared outcomes in prepectoral versus subpectoral prosthetic reconstruction after PMRT.[9,10] One study found that patients with prepectoral implants who received PMRT had lower rates of capsular contracture versus patients with subpectoral implants.[10] As implant coverage by the acellular dermal matrix (ADM) scaffold is larger in the prepectoral technique, surgeons have postulated that ADM may play a role in resisting contracture after radiation.[9,10]

Reasons for choosing different recon-
Disparities in reconstruction also exist when considering race and insurance status, because safety net hospitals often provide care to minorities as well as to the underserved and uninsured.[21] In a national retrospective cohort study, non-Caucasians were less likely to undergo immediate breast reconstruction or implant-based reconstruction compared to Caucasian patients.[22] In fact, 39.4% of Caucasians compared to 28% to 35.7% of non-Caucasians underwent immediate breast reconstruction.[22] Implant-based reconstruction was received by 85.5% of Caucasians compared to a lower frequency of 75.6% to 83.4% of patients receiving reconstruction depending on the minority group.[22] Furthermore, patients with no insurance were less likely to receive breast reconstruction overall.[18]

Researchers found minority race and lack of insurance to be associated with an increased use of PMRT, likely reflecting an advanced stage of presentation in this population.[19] Due to the increased use of radiation in this subset, physicians may be unwilling to offer immediate reconstruction in an effort to mitigate the increased complication rates seen with immediate implant-based reconstruction. Patients at safety net hospitals, however, often have other comorbid conditions that may not make them optimal surgical candidates for autologous reconstruction. In those who are more likely to receive PMRT and less likely to tolerate autologous reconstruction, patients are left with a choice between delayed autologous reconstruction and no reconstruction. As mentioned previously, immediate reconstruction of the breast leads to positive psychosocial benefits. An analysis of several studies utilizing Breast-Q, a quality-of-life assessment tool, found a consistent trend toward improved well-being and satisfaction in breast cancer patients receiving reconstruction.[23] Therefore, providers should make an effort to find alternate methods to reduce complications so that immediate implant-based reconstruction is still an option for these patients and disparities are reduced.

Conclusions and future directions
Breast reconstruction improves quality of life, but providers must be aware of the risks and benefits of each reconstruction approach in the setting of PMRT. The 2016 PMRT guideline update has served as a reminder for providers to revisit this topic. The uptrend in the use of reconstruction continues to reinforce the importance of collaboration among surgical oncologists, plastic surgeons, and radiation oncologists in regard to selecting the optimal approach to minimize complications in each patient. It is also important to recognize that there are limited data from nonacademic and safety net institutions on this topic. Further research and data collected from diverse institutions will help minimize disparities. With autologous reconstruction seemingly preferred at safety net hospitals and newer data showing less capsular contracture in prepectoral implant-based reconstruction, perhaps offering prepectoral implants in these patients is another method that can be used to minimize disparities in the type of reconstruction chosen at these institutions. As we move forward, a multidisciplinary discussion will continue to be at the forefront in finding ways to improve the quality of oncologic treatment delivered while minimizing associated complications in our breast cancer patients.

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

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For full reference list, visit cancernetwork.com/Postmastectomy-Radiotherapy
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In 2019, roughly 1.8 million people will be diagnosed with cancer in the United States. An estimated 268,600 women and 2,670 men will be diagnosed with breast cancer, which makes it the most common cancer diagnosis.1

Advances in treatment options, early detection, and prevention efforts have resulted in a steady decline in the rate of overall cancer deaths over the last 25 years. This decline has translated into more than 2 million fewer cancer deaths and has led to an increase in unique needs and challenges of cancer survivors and their caregivers.2

At a time when more people are surviving cancer than ever before, new paradigms of care, and perhaps even new definitions of survivorship, are needed. Addressing the most significant unmet needs of cancer survivors may lead to improved patient health outcomes and the ability to better manage long-term adverse effects. Guidelines and tools currently exist to support these efforts; however, implementation and utilization of these resources remain low. The most significant areas of unmet need in cancer survivorship include inconsistency in survivorship care planning and in transitions to primary care.2,3

Don S. Dizon, MD, reviews the issues that cancer survivors may encounter following diagnosis and treatment and suggests strategies that may assist in management. Dr Dizon also examines current views regarding the care of cancer survivors and discusses important issues that must be addressed so healthcare providers can reach the goal of improving the quality of life of this emerging population.

**Q:** What does survivorship mean and when does it start for patients?
**Dr Dizon:** I use the definition from the National Coalition for Cancer Survivorship, which is that you become a cancer survivor from the point of diagnosis. This definition is also inclusive of caregivers and anyone else who is touched by that individual’s cancer. So, it’s more of an encompassing definition than what’s typically thought of as survivors, who are patients who have completed first-line treatment with cure in mind. I think that definition has been fairly limiting.

**Q:** Who is a survivor? How many survivors are counted in the United States?
**Dr Dizon:** About 16 million people have lived through a diagnosis of cancer in the United States, and the expectation is that this number is going to grow to almost 22 million within the next decade. Now that’s just counting the folks who have been diagnosed with cancer. It’s clear that if the definition is more all-encompassing, it’s going to be far more people.1

**Q:** What is a survivorship care plan? Why is it necessary?
**Dr Dizon:** The survivorship care plan is intended to provide a roadmap for the present as one looks into the future. For patients who have completed first-line treatment, the plan typically consists of 2 significant parts. The first is the treatment summary, which is a coalition of the diagnosis, including what kind of cancer it was and how advanced it was when it was picked up; the treatment that was administered; and then the adverse effects that are present and those that might show up in the future. The second part gives direction for future care, whether that be in a primary care practice or within the oncology practice, and it includes guidance in terms of cancer-specific follow-up and also follow-up for other health conditions and further cancer screening.3

**Q:** What are the different “seasons of survivorship”? Why should they be considered dynamic?
**Dr Dizon:** The journey of cancer is quite a dynamic one. Often we speak of survivorship by means of seasons, and then it starts when someone is initially diagnosed; when they are undergoing treatment, that can be considered acute survivorship. And then once treatment is ended or they’re no longer in treatment, then an extended survivorship ensues in which risk of recurrence still exists. And then following that, if someone stays disease-free for a lengthy period of time, there may be this term of permanent survivorship. Now, there’s also the concept that patients may never be free from cancer and may be on extended treatments, whether that be a treatment to maintain a response, so-called maintenance therapy, or just ongoing cancer therapy in general. Also, one can sometimes call that period where someone goes from remission back into relapse a period of transitional survivorship. I do believe that this whole concept of extended survivorship needs to include patients who are not only just watching for a recurrence, but those patients who are on continuing therapy where there may not be an endpoint.3

**Q:** How do the needs of patients change across the different “seasons of survivorship”?
**Dr Dizon:** The needs of patients may change depending on whether or not they’re on active therapy. For example, if someone is newly diagnosed, their focus may be placed more on the diagnosis itself and the acute symptoms of treatment rather than on more extended concerns, whether that be children or even the needs of a partner, which tend to predominate once you’re through that acute period. Once a patient is through it and into sort of an extended or even a permanent survivorship, then their cancer-specific concerns may fade and issues of life in general outside of oncology do tend to predominate.1

**Q:** What are some of the most commonly used survivorship care models?
**Dr Dizon:** Well, there are several models of survivorship care in the United States. Some take the form of survivorship clinics, where patients who have been diagnosed with cancer can go in and actually have primary...
Q: How might cancer survivors benefit from a more precise definition of survivorship? How do you see survivorship plans evolving?

Dr Dizon: What I hope to see is that more people embrace the term of survivor, that it is not limited to patients who are completing curative-intent treatment. I do believe that everyone deserves a care plan. It’s probably not very useful for patients to receive a plan at one point in time and then never revisit it again. My vision for survivorship care as we look into the future and toward precision therapies, which are keeping patients stable for a long time, is that these care plans need to be more dynamic and they need to change as the seasons change within survivorship.

REFERENCES
Currently, chimeric antigen receptor (CAR) T-cell therapy is only approved as a standard of care for refractory or relapsed patients with adult B-cell non-Hodgkin lymphoma or childhood acute lymphoblastic leukemia. However, clinical trials have begun to evaluate it as a first- or second-line treatment. Studies are also being conducted to find CAR T-cells that may work in other forms of leukemia.

In an interview with CancerNetwork®, Mazyar Shadman, MD, MPH, discussed the study he and colleagues are conducting to evaluate CAR T-cell therapy in high-risk patients with chronic lymphocytic leukemia ahead of the 61st American Society of Hematology (ASH) Annual Meeting & Exposition, held December 7-10, 2019, in Orlando, Florida.

**Q:** What are you most looking forward to at ASH this year?

**DR. SHADMAN:** A lot of interesting studies, definitely in the lymphoma world, starting with results from specific antibody studies that will be presented, and specifically the one that we are still participating in: the CD20/CD3 bispecific antibody, mosunetuzumab. The study results will be presented as a poster at ASH; it was one of the top 6 abstracts for the whole meeting. It is a very promising drug and we are very excited to be a part of that study and we have had great responses. We are really hoping to see that drug moving forward and hopefully having it available to a lot of other patients outside of the trial after approval.

For lymphoma, we also have the CAR T-cell studies of course, in particular, the JCAR017 study coming out for large-cell lymphoma. As you know, there are 2 FDA-approved CAR T-cell therapies for diffuse large B-cell lymphoma, but JCAR017 is not currently approved for treatment. The study results that will be presented at ASH will show data which look very promising, with very similar efficacy, but probably a much better toxicity profile with CAR T-cell therapy. We are really hoping to get CAR T-cell therapy available for patients with large-cell lymphoma in the future, and that would be a very important addition to our toolbox to treat diffuse large B-cell lymphoma. So, that is another set of data to look at.

**Q:** Can you discuss your presentation?

**DR. SHADMAN:** At our institution, we have been treating patients with chronic lymphocytic leukemia (CLL) with CAR T-cell therapy in a clinical trial, so we have a lot of experience using this approach in these patients. Unfortunately, there are a significant number of patients who do not respond to CAR T-cell therapy or respond and later relapse, and so that makes it a unique patient population that are at high risk for relapse. That is a space where we need to know, first of all, the expectation, and how poorly this patient would do, because if you want to design any clinical trial to target this population you need to know the benchmark and where are you starting at so you can try to improve it. In this study, we looked at patients who had CLL and failed CAR T-cell therapy and we tried to have an understanding of their outcomes and how well or poorly they did with treatment. Also, we looked specifically at some of the characteristics that could define outcomes. This is kind of a unique study—the first in this space, retrospective, at a single institution, and a relatively small number of patients. I think this study is important, and we are already using these data to base some of the prospective trials that we are designing in this space and to make decisions in terms of the timing of referring patients for CAR T-cell therapy.

**Q:** Where are we in the field of CAR T-cell therapy and where do you think we are going?

**DR. SHADMAN:** I think we have made a lot of progress, the fact that we have 2 approved CAR T-cell therapies just for diffuse large B-cell lymphoma, it is a huge success. Right now, we are trying to get CAR T-cell therapy approved for different lymphoma histologies. The next step is to get CAR T-cell therapy approved for different lymphoma histologies. The next step is to get CAR T-cell therapy approved for different lymphoma histologies. The next step is to get CAR T-cell therapy available and have it as an option for patients with other types of lymphoma. That is the next line of studies, and a lot of them are already close to accrual, so this is a work in progress. The other focus is the setting in which CAR T-cell therapy is used, even for the approved currently approved indications. We first need to get the approval for other types of lymphoma. When that happens, we can try to use it in all kinds of settings, and not just refractory disease.
A 64-year-old white man was originally diagnosed with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) back in 2007. Initial presentation was with fatigue, elevated white blood cell counts with lymphocytosis, and a palpable lymph node in his neck. A biopsy of the neck node showed lymphoid infiltrates consistent with B-cell CLL that was later confirmed by flow cytometry. At initial presentation, he had favorable prognostic indicators including mutated immunoglobulin heavy chain gene (IgHV), negative zeta-associated protein kinase 70 kDa expression, and deletion of 13q14. He was managed with a watch-and-wait strategy until 2013 when he developed anemia (hemoglobin: 9.8 g/dL), mild thrombocytopenia (platelet count 116,000 per cubic mL) and an elevated white blood cell (WBC) count with lymphocytosis (WBC: 61,000 per cubic mL, with 79% lymphocytes). He was treated with 6 cycles of fludarabine, cyclophosphamide, and rituximab (Rituxan) with a complete clinical response. In 2015, work up for some respiratory symptoms discovered a 6 cm by 2.8 cm left upper lung mass. This turned out to be a T3 N0 M0 squamous cell non–small cell lung cancer (NSCLC) that was treated with 6 cycles of erlotinib, gemcitabine, and carboplatin. The patient presented with hypercalcemia (calcium: 13.5 mg/dL) and hypocalcemia (calcium: 4.5 mg/dL). He was treated with pamidronate and zoledronic acid with a symptomatic response. He underwent a cycle of gemcitabine and carboplatin with a partial response. He has been managed with pamidronate and zoledronic acid with stable disease. His current calcium level is 9.5 mg/dL with a normal parathyroid hormone level. Which of the following statements is/are true?

A. This clinical picture is consistent with the recurrence of squamous cell NSCLC with paraneoplastic hypercalcemia.

B. This clinical picture is consistent with the recurrence of CLL/SLL with Richter’s transformation leading to hypercalcemia.

C. This clinical picture is consistent with the recurrence of CLL/SLL with paraneoplastic hypercalcemia.

D. All of the above statements are true.
CORRECT ANSWER (B): This clinical picture is consistent with the recurrence of CLL/SLL with paraneoplastic hypercalcemia.

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ANSWER EXPLAINED: Bronchoscopy and biopsy of the subcarinal lymph node showed atypical lymphoid infiltrates consistent with CLL. Bone marrow aspiration and a biopsy revealed hypercellular bone marrow with CLL (Figure 2), and flow cytometry and cytogenetic evaluation revealed high CD38 expression and deletion of 17p. General treatment measures for hypercalcemia (intravenous hydration, furosemide, and bisphosphonates) were not effective until the start of ibrutinib (Imbruvica) and obinutuzumab (Gazyva). After 4 cycles of this regimen, the patient had a complete hematologic response, normalization of calcium levels, and a partial radiologic response to his lymphadenopathy.

Figure 2 Bone marrow showing near total replacement of normal hematopoietic elements by CLL (H&E; 40x magnification) (A) CLL cells in bone marrow (H&E, 1000x oil magnification (B)).

with curative intent left upper lobectomy followed by adjuvant chemotherapy with cisplatin and vinorelbine. In 2017, he presented with tiredness, axillary lymphadenopathy, anemia, elevated WBCs with lymphocytosis and thrombocytopenia. He was treated with 6 cycles of bendamustine and rituximab resulting in normalization of blood counts and a decrease in axillary, supraclavicular, and mediastinal lymphadenopathy which lasted 1 year.

In 2018, he presented with anorexia, vomiting, mild mental confusion, and weight loss. Further work up revealed hypercalcemia (Ca: 17.6 mg/dL, normal: 8.1–10.1 mg/dL), elevated WBC with lymphocytosis (WBC: 19.7 per cubic mL, with 81% lymphocytes), mild anemia (hemoglobin: 12.4 g/dL), and thrombocytopenia (platelet count 86,000 per cubic mL). Serum level of parathyroid hormone (PTH) was suppressed (PTH intact: 10 pg/mL, normal 12-65 pg/mL). The serum level of PTH-related peptide (PTHrP) was slightly elevated (PTHrP: 2.5 pmol/L, normal <2 pmol/L). The serum levels of vitamin D (25-hydroxyvitamin D: 25.6 ng/dL, normal: 30-61 ng/dL) and 1,25-dihydroxyvitamin D (1,25-dihydroxyvitamin D: 8.4 pg/mL, normal: 19.9-79.3 pg/mL) were both low. Serum thyroid-stimulating hormone and thyroxin levels were normal. Ultrasound of thyroid and parathyroid glands and a bone scan were normal. Computed tomography (CT) scans revealed enlarged lymph nodes in the bilateral neck, supraclavicular, mediastinum, hilum, central mesentery, aortocaval, and bilateral groin areas (Figure 1).

Outcome of This Case

Six months into his continued treatment with ibrutinib, the patient developed mild mental confusion, anorexia, and abdominal pain. Further evaluation revealed an elevated serum calcium level of 17.3 mg/dL, and CT scans revealed a mild to moderate increase in neck and chest lymphadenopathy and a large increase in abdomen.
CLINICAL QUANDARIES

HEMATOLOGIC MALIGNANCIES

Figure 3 CT scans revealing mild to moderate increase in neck and chest lymphadenopathy and large increase in abdomen lymphadenopathy.

and pelvis lymphadenopathy (Figure 3). A biopsy of a para-aortic node showed lymphoid tissue with B-cell CLL/SLL (Figure 4). The majority of cells in the biopsy specimen were small to intermediate in size with some scattered large cells. There were several areas with prolymphocytes and paraimmunoblasts consistent with proliferation centers. He was started on venetoclax (Venclexta) and had a short-lived clinical response lasting 1 month. Coincidentally, with disease progression, hypercalcemia reappeared. A bone marrow biopsy showed hypercellular bone marrow with atypical lymphoid proliferation with large cells concerning for Richter’s transformation (Figure 5). He was evaluated for chimeric antigen receptor T-cell therapy; however, his underlying disease progressed rapidly. The patient and family decided on hospice care. His overall condition deteriorated with persistent refractory hypercalcemia and he passed away shortly thereafter.

Discussion

Here we present a patient with 2 distinct primary cancers, CLL/SLL and squamous cell NSCLC, who developed rather refractory hypercalcemia that eventually led to his death.

The differential diagnosis of hypercalcemia includes multiple pathologic entities, but the 2 most common etiologies include primary hyperparathyroidism and hypercalcemia of malignancy. The estimated yearly prevalence of hypercalcemia for all cancers is nearly 3%. Hypercalcemia is 4 times more common in stage IV cancer and it is associated with a poor prognosis. The most common cancers presenting with malignant hypercalcemia are lung cancer, multiple myeloma, and renal cell carcinoma. These are followed by breast and colorectal cancers, and the lowest rates are reported in prostate cancer. Hypercalcemia of malignancy is a relatively frequent finding in patients with cancer, affecting almost half of patients, particularly in those with advanced stage cancer. Patients with hypercalcemia of malignancy tend to have limited survival of several months, and it is not clear whether this poor prognosis is related to the advanced stage of malignancy or if hypercalcemia is simply a marker of more aggressive cancer.

Key Points

• Hypercalcemia of malignancy is a relatively frequent finding in patients with cancer affecting nearly half of patients, particularly in those with advanced stage cancer and limited survival of several months. It is not clear whether this poor prognosis is related to the advanced stage of malignancy or if hypercalcemia is simply a marker of more aggressive cancer.
• Hypercalcemia in B-cell CLL/SLL is extremely rare. Proposed mechanisms for hypercalcemia include concurrent primary hyperparathyroidism, secondary hyperparathyroidism related to tumor production of vitamin D (1,25-dihydroxycholecalciferol) or PTHrP, or secondary osteolysis by an osteoclast-activating factor such as TNF-alpha.
• Hypercalcemia of B-cell CLL/SLL has also been observed in patients with transformation of CLL to prolymphocytic leukemia or large-cell (immunoblastic) lymphoma (Richter’s syndrome). The presumed pathogenesis of hypercalcemia is the release of serum cytokines TNF-alpha and IL-6, which are thought to increase bone resorption.
by parathyroid carcinoma and extra-parathyroid malignancies, and hypercalcemia due to paraprotein binding. Approximately 80% of malignancy-related hypercalcemia is mediated by the production of PTHrP. PTHrP is normally produced and secreted by various cells, including normal breast cells, and participates in the development of various tissues. PTHrP acts on osteoblasts, leading to enhanced synthesis of receptor activator of nuclear factor-kappa B ligand, with subsequent activation of osteoclasts and bone resorption with calcium release into the blood stream and increased renal calcium reabsorption. Squamous cell cancers, urinary tract cancers (renal cancer and bladder cancer), breast cancer, non-Hodgkin lymphoma, and ovarian cancer account for the majority of malignancies leading to hypercalcemia through PTHrP.

Hypercalcemia develops in 6% of patients with lung cancer. Squamous cell carcinoma is the most frequent type of lung cancer in patients with hypercalcemia. In patients with lung cancer, hypercalcemia is more commonly caused by tumor secretion of PTHrP. Our patient had an early stage (T3N0M0) squamous NSCLC that was treated with curative intent. Radiologic findings, bronchoscopy, and biopsy of a subcarinal lymph node all supported the diagnosis of recurrent CLL/SLL rather than recurrent lung cancer.

Hypercalcemia in B-cell CLL is extremely rare, with less than 30 cases reported in the English literature in the past 50 years. In a retrospective study of 1200 patients with B-cell CLL, only 7 patients (0.006%) were found to have high calcium levels. Proposed mechanisms for hypercalcemia in patients with CLL include concurrent primary hyperparathyroidism, secondary hyperparathyroidism related to tumor production of vitamin D (1,25-dihydroxycholecalciferol) or PTHrP, or secondary osteolysis by an osteoclast-activating factor such as tumor necrosis factor-alpha (TNF-alpha). The mechanism of dysregulated production of vitamin D (1,25-dihydroxycholecalciferol) has been postulated to be similar to that of hypercalcemia due to sarcoidosis; however, it has not been clarified if the primary source of 1,25-dihydroxycholecalciferol is leukemia cells or surrounding macrophages in this setting. Hypercalcemia of CLL has also been observed in patients with transformation of CLL to prolymphocytic leukemia or large-cell (immunoblastic) lymphoma (Richter’s syndrome). The presumed pathogenesis of hypercalcemia is the release of serum cytokines TNF-alpha and interleukin 6 (IL-6), which are thought to increase bone resorption. It has also been reported that hypercalcemia in CLL can occur without any of the above mechanisms.

In our case, the low serum PTH, low PTHrP, and normal vitamin D (1,25-dihydroxycholecalciferol) levels, without any other solid tumor, support that hypercalcemia was not the result of a primary or secondary hyperparathyroid state. It is also unlikely that the hypercalcemia in our patient was secondary to osteolysis due to lack of extensive bony involvement. While the initial presentation with hypercalcemia showed no signs of Richter’s transformation, later in the course of his disease, the patient became refractory to treatment and a bone marrow sample at that point confirmed large-cell transformation with Richter’s syndrome.

Here, we present a very rare case of...
B-cell CLL/SLL in a patient who presented with symptomatic hypercalcemia. The patient initially responded to treatment but progressed within 6 months and his disease transformed into Richter’s syndrome with a dismal outcome. Future research on the pathogenesis of hypercalcemia in CLL will increase our understanding of this rare complication and potentially help discover appropriate management options for these patients.

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Molecular Characterization and Treatment of Pancreatic Neuroendocrine Tumors

ONCOLOGY recently spoke with Ana Maria Cristina De Jesus-Acosta, MD, an assistant professor of oncology at Johns Hopkins University, about the molecular characterization and treatment of pancreatic neuroendocrine tumors.

Q: What are pancreatic neuroendocrine tumors, and how frequently are patients typically diagnosed at an earlier or later stage?

DR. DE JESUS-ACOSTA: Neuroendocrine tumors are tumors that arise within the neuroendocrine tissues of the gastrointestinal tract or the pulmonary tract. However, when they originate from the islets of Langerhans within the pancreas, we call them pancreatic neuroendocrine tumors. This is not a very common tumor type compared with other cancers. Pancreatic neuroendocrine tumors occur in approximately 1 to 3 cases for every 100,000 individuals per year in the United States. These tumors also account for around 1% to 2% of all newly diagnosed pancreatic tumors. Certainly, with improvements in medical imaging techniques and an increased number of diagnostic procedures, we are identifying these tumors more often. Most patients do not have symptoms early on, so it’s not until later, when they have advanced disease or metastatic disease, that they tend to develop symptoms and seek medical guidance. Therefore, most of the patients we see have stage IV disease at the time of presentation.

Q: What have we learned about the molecular biology of this tumor type?

DR. DE JESUS-ACOSTA: Most of the knowledge that we have about the mutations and pathways involved in the biology of pancreatic neuroendocrine tumors comes from genomic exome sequencing results that were originally reported in 2011. The most frequent somatic mutations that have been identified occur in genes that encode for proteins implicated in chromatin remodeling. Approximately 44% of these tumors have a somatic inactivating mutation in a gene called MEN1, which is a tumor suppressor gene, and is linked to the menin pathway. There are around 43% of pancreatic neuroendocrine tumor cases that have mutations in the genes that encode for either a transcription or chromatin remodeling complex composed of death-domain associated protein, also known as DAXX, and the thalassemia/mental retardation syndrome X-linked, which is called ATRX. This is also called the DAXX/ATRX pathway implicated in this disease. More importantly, around 14% of patients will have mutations in the genes that are key in the mammalian target of rapamycin, also known as the mTOR pathway, and mutations in the phosphatidylinositol 3-kinase pathway. Pancreatic neuroendocrine tumors are highly vascular tumors, so angiogenesis pathways are also very important for this disease. VEGF is expressed in approximately 78% to 80% of patients with pancreatic neuroendocrine tumors. Knowledge of the molecular biology in pancreatic neuroendocrine tumors is very important and has clinical implications. For example, everolimus (Afinitor), which is an mTOR inhibitor, is now approved by the FDA for all patients with neuroendocrine tumors, including pancreatic...
primary tumors. Another agent, sunitinib (Sutent), that targets the VEGF receptor is also approved by the FDA specifically for patients with pancreatic neuroendocrine tumors, after a large phase III study noted improvement in progression-free survival in patients given sunitinib compared with placebo. Similarly, there are other agents that target the VEGF receptor. These are being tested at different stages in clinical trials. We have results for some and are still waiting for the results of other clinical trials.

Q: You mentioned some of the therapies used to treat patients with pancreatic neuroendocrine tumors. What are the initial, frontline therapy options and are there variations in therapies based on the biology and genetics of the tumor?

DR. DE JESUS-ACOSTA: This depends on the initial stage at presentation. Ideally, we want to see these patients in a multidisciplinary clinical setting, along with medical oncologists, surgeons, interventional radiologists, and other physicians. For patients that have resectable disease or locoregional disease, surgery is used as upfront therapy and is recommended with a curative intent. For patients with locally advanced but unresectable disease or stage IV metastatic disease that is not amenable for resection, we offer systemic therapies upfront as the preferred approach. Among the different types of systemic therapies, somatostatin analogues are most commonly used upfront. Most patients with pancreatic neuroendocrine tumors or any neuroendocrine tumors in general have high expression of somatostatin receptors. As such, when we use somatostatin analogues, we can delay progression in patients with pancreatic neuroendocrine tumors and we have shown that improves symptoms in those with functional neuroendocrine tumors or functional pancreatic neuroendocrine tumors. Another agent that can be used in the frontline setting is everolimus, which is also preferred for those patients that do not express somatostatin receptors. As of now, the genetics of an individual patient or the molecular pathways of an individual patient are not used to select a therapy upfront, but this may be an area of investigation down the road.

Q: Based on what we know about the molecular biology of these tumors, are there any investigational targeted agents being tested in clinical trials for subsets of patients with pancreatic neuroendocrine tumors?

DR. DE JESUS-ACOSTA: It is very difficult to do clinical trials specifically for certain molecular subtypes in patients with pancreatic neuroendocrine tumors, primarily because these types of tumors have a very low incidence. If we subclassify or subdivide patients based on the molecular profiling, we may not have enough patients to enroll them very quickly in a clinical trial. In general, clinical trials allow patients with any type of neuroendocrine tumor to participate or we can do clinical trials specifically for pancreatic neuroendocrine tumors without limiting them to specific molecular subtypes. On the other hand, there are other ongoing trials such as NCI-MATCH that can assign patients to a specific therapy based on the genetic changes found in these tumors through genetic sequences for individual patients. This approach seeks to determine whether cancer treatment based on its specific genetic changes is effective irrespective of the primary cancer type. For patients with pancreatic neuroendocrine tumors, if you know there are certain specific mutations or some pathways that are expressed based on genomic sequencing, you can refer these patients to the NCI-MATCH study, but we do not have clinical trials that are specifically for molecular subtypes in pancreatic neuroendocrine tumors.

Q: Are there other clinical trials of drugs for these patients, specific for pancreatic neuroendocrine tumors or ones that include these patients among others, that are showing some signs of efficacy or have a novel mechanism of action that you could highlight?

DR. DE JESUS-ACOSTA: Yes, there is significant interest in a drug called cabozantinib (Cabometyx). It is a tyrosine kinase inhibitor that targets multiple pathways, including VEGF and c-Met, which are important for pancreatic neuroendocrine tumors and neuroendocrine tumors in general. There is a phase II study that demonstrated promising results in pancreatic neuroendocrine tumors and other carcinoid tumors with...
Pancreatic neuroendocrine tumors (pNETs) are uncommon but their incidence in the United States has tripled in the last 2 decades, likely owing to earlier and incidental diagnoses. Multiple systemic treatment agents have activity but the optimal sequence of therapies in patients with advanced disease is not known. With the introduction of peptide receptor radionuclide therapy (PRRT), treatment has become more complicated and there is a need for comparative studies of the available agents. Although PRRT has yet to be prospectively investigated in pNETs, multiple retrospective studies suggest good efficacy with favorable progression-free survival. There is also a need for a better understanding of how genomic alterations may predict outcomes of different therapies.

Whole-genomic sequencing has shown that pNETs have a unique genetic landscape compared with their exocrine counterpart and small bowel NETs. For example, compared with small bowel NETs, pNETs carry a significantly higher frequency of mutations in MEN1, FOXO3, ATRX, and TSC2 genes. A recent study also showed that sporadic pNETs frequently harbor germline mutations, including mutations in the DNA repair genes MUTYH, CHEK2, and BRCA2. Overall, more than half of pNETs carry somatic mutations at the ATRX, DAXX, or MEN1 (A-D-M) genes, which is associated with inferior prognosis compared with A-D-M wild-type status. This A-D-M status (mutated vs wild) can potentially be helpful in stratifying the prognosis of well-differentiated pNETs and aid in counseling patients. However, results of studies published thus far have been somewhat discordant, perhaps due to the disease stage of the cohorts that were analyzed. Loss of function of ATRX and DAXX is associated with alternative lengthening of telomeres (ALT), which can be conveniently detected with fluorescence in situ hybridization, is associated with an increased risk of metastases in small pNETs, and may be a useful tool to predict outcomes following resection. Further validation of ALT as a prognosticator is needed.

The identification of alterations of these pathways may have important therapeutic implications in terms of developing novel systemic therapies for pNETs and improving upon currently known active drugs in pNETs (eg, everolimus with mTOR inhibition). While the reported alterations do not yet routinely inform treatment decisions, genomic predictors of outcomes should be incorporated in future prospective trials of therapies for pNETs as correlative studies.

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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.

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