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October 2018
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LifeBridge
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I’m sitting at Gate 34 at the airport in Austin, TX. My flight is delayed and I don’t know when I’m going to get on this plane. I’ve been on the road for work for a week, the 2019 budget is due, and I need to write this article. I’m a little stressed… …and my stress level is 1/10th of what you as a physician deal with on a daily basis.

As the CEO of the Duval County Medical Society (DCMS), it is my honor and privilege to serve on the Board of the American Association of Medical Society Executives. In this capacity, I am able to work with Executives from the American Medical Association, State Medical Associations, and County Medical Societies across the United States.

This week, this group has been meeting to share best practices in helping our members reduce stress and return to the joy of medicine. The LifeBridge Physician Wellness Program offered by the DCMS is a nationally recognized best practice. I was happy to share the successes of our program in working with many physicians to cope with stress, burnout and the myriad of issues physicians deal with on a daily basis.

However, I was equally concerned to hear about the impact of a recent article on KevinMD entitled Physician Wellness Programs are Lipstick on a Pig, which is causing a stir in the physician community.

The article posits that Physician Wellness Programs don’t do anything to actually help physicians. It says that the problem is solely burdensome regulation, cumbersome electronic health records, and a system that abuses physicians.

I disagree. Those concerns are specifically why LifeBridge is different than other programs, and why the DCMS is taking a leading role in reducing physician burnout.

LifeBridge is a free, confidential service which provides any DCMS member access to a counselor for up to six free confidential sessions per calendar year. Our program is approved by the Florida Board of Medicine and does NOT create any medical record. Utilization of the program will not be reported to your insurance, your program is approved by the Florida Board of Medicine and does NOT create any medical record. Utilization of the program will not be reported to your insurance, your employer, the Medical Society, or the Board of Medicine. Sessions are conducted in person in one of several convenient and private locations throughout the city.

If you are experiencing stress or burnout… or even if you are concerned that you might be at the early stages of burnout; if you are dealing with stressful times in your household; if you are concerned that you may want to leave medicine because you’ve lost the joy; if any of these scenarios apply to you, PLEASE, do what so many of your colleagues have done and take advantage of this free resource.

Lipstick on a pig?

This is more than someone telling you to be mindful while still holding you accountable for a never-ending deluge of digital paperwork. This is the opportunity for you to truly take the time to focus on your own well-being. But what about all of that burdensome regulation? Until that goes away, I’ll always be stressed at work.

This is where the power of being involved in organized medicine truly matters. The DCMS has a number of delegates who are actively involved in the Florida Medical Association (FMA) and the American Medical Association (AMA). Both of these groups are relentlessly working to help guide the ever-changing healthcare landscape to be less burdensome on physicians.

They are also constantly vigilant in protecting physicians from regulations which would do real harm to physicians. A very recent example was the Proposed CMS Rule which would “simplify” E/M codes for physicians, but also reduce reimbursement for a majority of those codes. The AMA, FMA and DCMS all came out strongly in opposition to this proposed rule, with hundreds of member physicians submitting comment to modify the proposed rule.

For 165 years, the DCMS has been fighting for the physicians of Jacksonville and we’ll continue to fight for you every day. All that I personally ask in return is that you continue taking care of the health of our community… and that starts with yourself.
Progress in the management of metastatic breast cancer in 2018: Is a cure in the horizon?

Background:
The Duval County Medical Society (DCMS) is proud to provide its members with free continuing medical education (CME) opportunities in subject areas mandated and suggested by the State of Florida Board of Medicine to obtain and retain medical licensure. The DCMS would like to thank the St. Vincent’s Healthcare Committee on CME for reviewing and accrediting this activity in compliance with the Accreditation Council on Continuing Medical Education (ACCME).

This issue of Northeast Florida Medicine includes an article, “Progress in the management of metastatic breast cancer in 2018: Is a cure in the horizon?” authored by Gerardo Colón-Otero, MD, which has been approved for 1 AMA PRA Category 1 credit.™ For a full description of CME requirements for Florida physicians, please visit www.dcmsonline.org.

Faculty/Credentials:
Gerardo Colón-Otero, MD, Professor of Medicine, Mayo Clinic College of Medicine, Vice-Dean, Mayo Clinic School of Medicine, Dean, Florida Campus, Mayo Clinic School of Medicine.

Objectives:
1. List the drugs approved over the last six years for the treatment of metastatic breast cancer.
2. Describe the biomarkers used for the selection of treatments for patients with metastatic breast cancer.
3. State the names of promising new drugs currently being evaluated for the management of metastatic breast cancer.

Date of release: Oct. 1, 2018 Date Credit Expires: Oct. 1, 2020 Estimated Completion Time: 1 hour

How to Earn this CME Credit:
1) Read the “Polypharmacy; A Case-based Primer on the Practice in the Geriatric Population” article.
2) Complete the posttest. Scan and email your test to Kristy Williford at kristy@dcmsonline.org.
3) You can also go to www.dcmsonline.org/NEFMCE to read the article and take the CME test online.
4) All non-members must submit payment for their CME before their test can be graded.

CME Credit Eligibility:
A minimum passing grade of 70% must be achieved. Only one re-take opportunity will be granted. If you take your test online, a certificate of credit/completion will be automatically downloaded to your DCMS member profile. If you submit your test by mail, a certificate of credit/completion will be emailed within four weeks of submission. If you have any questions, please contact Kristy Williford at 904-355-6561 or kristy@dcmsonline.org.

Faculty Disclosure:
Gerardo Colón-Otero, MD reports grant/research support from Novartis to Mayo Clinic for Investigator Initiated Trial.

Disclosure of Conflicts of Interest:
St. Vincent’s Healthcare (SVHC) requires speakers, faculty, CME Committee and other individuals who are in a position to control the content of this educational activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly evaluated by SVHC for fair balance, scientific objectivity of studies mentioned in the presentation and educational materials used as basis for content, and appropriateness of patient care recommendations.

Joint Sponsorship Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of St. Vincent’s Healthcare and the Duval County Medical Society. St. Vincent’s Healthcare designates this educational activity for a maximum of 1 AMA PRA Category 1 credit.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.
Progress in the management of metastatic breast cancer in 2018: Is a cure in the horizon?

By Gerardo Colón-Otero, MD, Mayo Clinic, Florida

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Abstract

Progress in the management of breast cancer over the last 40 years has resulted in a decrease in breast cancer mortality and morbidity. Major advances include the significant prolongation of life in patients with HER2 positive subset breast cancers and the addition of multiple new agents for the treatment of the most common type of breast cancer, namely the Estrogen Receptor (ER) positive subtype. The identification of the BRCA genes as the main causes of inherited breast cancer, and the identification of drugs that are particularly effective in this subset of patients has also resulted in improved outcomes. Recent findings suggest that checkpoint inhibitors have significant synergism with chemotherapy in the neo-adjuvant setting. Immuno-conjugate drugs for the triple negative breast cancer sub-group are showing significant activity in the refractory setting. The authors predict that the effective personalized combination of these targeted treatments will likely result in the cure of the majority of metastatic breast cancer patients in the next 15 years.

Introduction

It has been 40 years since the United States Food and Drug Administration (FDA) approved tamoxifen, an oral medication that targets the estrogen receptor which is expressed in over 80 percent of breast cancer cases. Since then, over a million women in the United States (U.S.) in the prime of their lives have succumbed from metastatic breast cancer. Over the past five years, there has been a marked acceleration in drug development against cancer propelled by advancements in basic science, particular molecular biology. A total of eight new targeted drugs against metastatic breast cancer have been FDA approved over the last six years, which is more than the number of drugs approved over the preceding 30 years (Table 1).

Table 1: Timeline of the development of new agents for the treatment of breast cancer since 1977

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approval</th>
<th>Mechanism of action/Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>1977</td>
<td>Competitive inhibitor of ER/ER positive</td>
</tr>
<tr>
<td>Exemestane</td>
<td>1999</td>
<td>Aromatase inhibitor/ER positive</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>2000</td>
<td>Aromatase inhibitor/ER positive</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>2002</td>
<td>Competitive inhibitor of ER/ER positive</td>
</tr>
<tr>
<td>Letrozole</td>
<td>2004</td>
<td>Aromatase inhibitor/ER positive</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2006</td>
<td>monoclonal antibody against HER2/HER2 positive</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>2007</td>
<td>tyrosine kinase inhibitor of HER2/HER2 positive</td>
</tr>
<tr>
<td>Everolimus</td>
<td>2012</td>
<td>mTOR inhibitor/ER positive</td>
</tr>
<tr>
<td>TDM-1</td>
<td>2013</td>
<td>immuno-conjugate binds to HER2/HER2 positive</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>2013</td>
<td>monoclonal antibody against HER2/HER2 positive</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>2016</td>
<td>Cyclin kinase inhibitor/ER positive</td>
</tr>
<tr>
<td>Neratinib</td>
<td>2017</td>
<td>tyrosine kinase inhibitor of HER2/HER2 positive</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>2017</td>
<td>Cyclin kinase inhibitor/ER positive</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>2017</td>
<td>Cyclin kinase inhibitor/ER positive</td>
</tr>
<tr>
<td>Olaparib</td>
<td>2018</td>
<td>ARP inhibitor/BRCA mutated</td>
</tr>
</tbody>
</table>

Breast cancer is the most common cancer in women in the U.S. with more than 240,000 cases per year and over 40,000 deaths per year. Data has shown significant heterogeneity among individual breast cancer cases, particularly in the metastatic setting, which significantly contributes to the almost universal development of treatment resistance and eventual patient’s demise. Despite this, there are multiple reasons to be optimistic, including the fact that new drugs with new mechanisms of action are being developed. It is important to understand the data on recently approved drugs and promising new agents against metastatic breast cancer. The data on these agents suggest that the elusive goal of achieving cures for the majority of patients with metastatic breast cancer may be within reach in the next 15 years.

Recent progress: A look into a promising future

Estrogen Receptor positive disease

The discovery of tamoxifen and the aromatase inhibitors led to a marked improvement in the outcome of patients with metastatic ER positive breast cancer. The m-TOR
inhibitor everolimus received FDA approval in 2012 based on the results of the BOLERO2 clinical trial which showed a significant prolongation of progression free survival in the group treated with exemestane and everolimus compared with exemestane as a single agent. The last few years have seen the introduction of the cyclin kinase inhibitors (palbociclib, ribociclib and abemaciclib) which nearly doubled the time before progression in the upfront and second line setting treatment for metastatic ER positive breast cancer in combination with anti-estrogen treatments. There will likely be development of additional combinations for the treatment of metastatic ER positive breast cancer and the identification of the mutations associated with drug resistance. The discovery of the Estrogen Receptor activation mutations (ESR1 gene mutations in the ligand binding domain) and their associated resistance to aromatase inhibitors will likely lead to the personalized initial treatment of ER positive metastatic breast cancer and the selection of the estrogen receptor degrading inhibitor, fulvestrant or other anti-estrogen agents, over the aromatase inhibitors in this subset of patients. The ISPY 2 trial showed marked improvement in pathological complete remission (pCR) with the upfront neoadjuvant addition of pembrolizumab to paclitaxel (an increase in pCR from 19 percent to 39 percent) in ER positive HER2 negative tumors. These results suggest that the early incorporation of pembrolizumab and paclitaxel in the neo-adjuvant treatment of patients with locally advanced ER positive breast cancer will likely result in improved outcomes. Studies incorporating all of these agents may be feasible given the differences in toxicities associated with these agents. It is likely that these new combinations may result in a greater percentage of patients with metastatic ER positive breast cancer achieving long term control of their disease if not cures.

**HER2 amplified breast cancer**

Up to one in every four women with breast cancer will harbor tumors with amplification of the HER2 gene. These patients used to have the poorest prognosis among all breast cancer subsets, even worse than that of the triple negative subset, until the introduction of trastuzumab. Trastuzumab is a monoclonal antibody that targets the HER2 protein and which was shown to significantly improve survival among patients with HER2-amplified metastatic breast cancer. The level of improvement by the addition of trastuzumab to chemotherapy was so significant that it resulted in outcomes that were similar to that of patients with metastatic ER positive HER2 negative tumors, the subset with the best prognosis. The subsequent addition of pertuzumab to trastuzumab and chemotherapy in patients with metastatic HER2 positive breast cancer in the Cleopatra trial, led to further significant improvements in overall survival. The subset of HER2 amplified breast cancers with increased infiltration of lymphocytes in the tumor had the best response to the combined monoclonal antibodies treatment with up to 40 percent of these patients been free of tumor progression at five years, which represents a remarkable achievement. These findings suggest the possibility of significant synergism between combined monoclonal antibodies and checkpoint inhibitors and implies that this combination could potentially lead to a cure for the majority of these patients. The development of the immune-conjugate TDM-1, led to significant improvements in progression free survival and overall survival in the second line setting as compared with the combination of lapatinib and capecitabine. The development of new, more effective tyrosine kinase inhibitors (neratinib and pyrotinib) is likely to even further improve these outcomes. The newer tyrosine kinase inhibitors are showing significant clinical activity against metastatic disease involving the brain, a common complication in the HER2 positive breast cancers seen in up to 50 percent of these patients. The newer immune-conjugate, trastuzumab deruxtecan, has been associated with over 60 percent response rates in patients who failed trastuzumab, pertuzumab and TDM-1. These levels of activity are likely to translate into significant improvements in overall survival when these agents are used in the upfront setting. Finally, the checkpoint inhibitor pembrolizumab has shown significant activity with a 15 percent response rate in patients who failed multiple previous systemic treatments including trastuzumab, when added to trastuzumab treatment. Given this finding, one could predict significant synergism of pembrolizumab when given in the upfront setting in combination with chemotherapy and dual HER2 inhibition with pertuzumab and trastuzumab. It is quite likely that combination treatments that incorporate the novel tyrosine kinase inhibitors with the newer immuno-conjugates and
checkpoint inhibitors will potentially lead to long term control or cure in a significantly higher percentage of patients with metastatic HER2 amplified breast cancer.

**Triple negative Breast Cancer**

Tumors that do not express ER and Progesterone Receptor (PR) and do not have amplifications of the ERB2 (HER2) gene (called triple negative breast tumors) have the worst prognosis. These tumors are more common in younger patients, in patients with germline BRCA1 mutations, and in African American, Hispanic and Native American subjects. Standard of care for these patients consists of systemic chemotherapy, with most patients eventually progressing and dying from their disease. In 2018, olaparib, a Poly (ADP-Ribose) Polymerase (PARP) inhibitor, became the first drug approved for the treatment of metastatic breast cancer in patients with germline BRCA mutations and HER2 negative metastatic breast cancer including triple negative breast cancer, given the findings of greater response rates with less toxicity than single agent chemotherapy. Based on the results of the use of these agents in BRCA mutated high grade serous carcinomas of the ovaries, tumors that are genetically similar to triple negative breast cancer, it is likely that the use of these agents as maintenance therapy earlier in the management of metastatic BRCA mutated triple negative breast cancer will likely translate into even greater benefit. Talazoparib is another PARP-inhibitor that will likely be approved for breast cancer in the near future based on the results of the phase 3 EMBRACA trial that showed a significantly higher response rate and duration of treatment response as compared with chemotherapy.

Immuno-conjugates are another promising new treatment for metastatic triple negative breast cancer. These agents consist of a monoclonal antibody targeting a protein expressed by the triple negative breast cancer cells, attached to a chemotherapeutic agent. Three of these agents are currently undergoing phase 3 clinical trial evaluations and are likely to be approved for clinical use in the near future. Glembatumumab vedotin targets the transmembrane glycoprotein NMB (osteocactinin) which is expressed in over 25 percent of breast cancers. A 30 percent response rate was observed in a phase 2 trial of refractory triple negative breast cancer. A phase 3 trial of glembatumumab versus capecitabine is currently underway. Ladiratuzumab vedotin targets the LIV-1 transmembrane protein that is expressed by over 90 percent of breast cancers. A 25 percent response rate was observed in 63 patients with metastatic breast cancer who had failed a median of four prior chemotherapies. Sacituzumab govitecan is an immuno-conjugate of an anti-TROP-2 antibody linked to SN-38 which is the active metabolite of irinotecan. TROP-2 is a surface glycoprotein expressed in over 90 percent of breast cancers. A 34 percent response rate was observed in 110 patients with metastatic breast cancer who had failed two or more previous chemotherapies. The toxicity profile of PARP inhibitors, checkpoint inhibitors, and the immune-conjugates suggest that combination treatment with these agents may be feasible and could possibly be synergistic. If so, this may translate into significant improvement in overall survival and potential cures.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Breast cancer subset</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrotinib</td>
<td>HER2 positive</td>
<td>TK inhibitor HER2</td>
</tr>
<tr>
<td>Trastuzumab deruxtucan</td>
<td>HER2 positive</td>
<td>immuno-conjugate</td>
</tr>
<tr>
<td>Sacituzumab govitecan (Immu-132; anti-Trop-2)</td>
<td>triple negative</td>
<td>immuno-conjugate</td>
</tr>
<tr>
<td>Glembatumumab vedotin (anti- GP-NMB)</td>
<td>triple negative</td>
<td>immuno-conjugate</td>
</tr>
<tr>
<td>Ladiratuzumab vedotin (anti-LIV-1 with MMAE)</td>
<td>triple negative</td>
<td>immuno-conjugate</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>triple negative</td>
<td>PD1 monoclonal AB</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>BRCA mutated</td>
<td>PARP inhibitor</td>
</tr>
</tbody>
</table>
Conclusion

Over the last six years, new agents have been approved for the treatment of breast cancer than over the preceding 35 years, a result of amazing advancements in molecular biology over the last decade. Currently, at least seven agents with promising preliminary results will likely become FDA approved over the next few years. The expansion of knowledge of the causes of tumor resistance to targeted agents will translate into the development of new agents that could bypass the resistance mechanisms. It is hoped that these developments will translate into cures so that the untimely loss of over 40,000 women in the prime of their lives per year in the U.S. alone can be prevented.

References