ACKNOWLEDGEMENTS

We would like to give a huge thank you to Dr. Clemmons, our amazing editors from NCODA, and our hard-working pharmacy students for their contributions in making this edition an amazing one!
This past summer SOAP merged with an associated affiliate, National Community Oncology Dispensing Association (NCODA), a medically-integrated professional student organization. They have provided us immense support, including editors for this newsletter, and we are grateful for the opportunities now available to our chapter. We were also able to host a few of their leaders for a UGA Football game!

This semester was filled with many exciting events and we welcomed the incoming P1 class to our SOAP family! We hosted two booths at Pharmtoberfest, an annual community-centered event held by the College of Pharmacy. We educated students on important screening guidelines, risk factors, and how to detect a potential breast cancer mass. We also partnered with DKMS- a global nonprofit dedicated to fighting against blood cancers and disorders- to swab volunteers for potential bone marrow donations! If matched, they will be able to donate to a cancer patient needing a bone marrow transplant. It was very successful as we tested over 35 students and professors. Our Community Outreach Chair, Erin Weippert, played a huge role in coordinating our events and we are super grateful for dedicated members such as her.

As October was Breast Cancer Awareness Month, we held an incredible panel that was not only inspiring but deeply grounding. Our beautiful speakers included breast cancer fighters pictured here (left to right): Dr. Vivia Hill-Silcott, Dr. Michelle McElhannon, Mickey Yongue, Dawn Burden, and Louise Huff, while Dr. Grace Gowda was present via zoom. Thank you all for being so strong and sharing your stories.
Background

Glioblastoma is a brain tumor that accounts for around 47.7% of all CNS tumors, with an incidence of roughly 10,000 patients per year in the United States.¹ Despite its prevalence in the U.S., the prognosis for many glioblastoma patients is poor. The average length of survival for patients with glioblastoma is eight months, with a discouraging five-year survival rate of 6.8%.² These poor outcomes have encouraged researchers to examine the role of promising immunotherapy treatments in glioblastoma, done with the hope of curtailing its mortality and improving the lives of glioblastoma patients worldwide.

Glioblastoma is a cancer that affects astrocytes in the brain. Astrocytes are a class of glial cells responsible for maintaining the normal functioning of neurons. Glioblastomas aggressively infiltrate surrounding brain tissue, with the consequences of rapid, uncontrolled astroglial division in the brain contributing to its significant mortality. The standard of care for glioblastoma varies by patient and by tumor heterogeneity, but typically consists of radiotherapy, surgery, and an alkylating agent known as temozolomide.³ Four novel immunotherapy candidates will be discussed in the sections that follow.

Immune checkpoint inhibitors

Used successfully in melanoma and non-small cell lung cancer, immune checkpoint inhibitors (ICIs) promote T-cell activation through a number of mechanisms. By antagonizing CTLA-4 or PD-1 receptors on cytotoxic (CD-8) T-cells and regulatory T-cells, ICIs disrupt T-cell suppression related to chronic inflammation, increasing their activity against tumor cells. Phase I results from the Checkmate 143 trial showed signs of promise for nivolumab (anti-PD-1) as an agent for recurrent glioblastoma, though phase III results did not show an improvement in overall survival compared to bevacizumab.⁴ A similar failure to achieve the primary endpoint was observed for pembrolizumab.⁵ Glioblastoma tumors are known to adapt to ICI antagonism, which may further limit the use of ICIs in patients with glioblastoma. Importantly, glioblastoma usually contains few T-cells and an overwhelming amount of myeloid suppression, decreasing tumor cell responsiveness to ICIs. Current standard of care treatment with temozolomide may also exacerbate T-cell immunosuppression, further reducing the efficacy of ICIs.

Myeloid-targeted therapies

Macrophages play an important role in the development of glioblastoma. An intricate cascade mediated by tumor-associated microglia (TAMs) is responsible for promoting tumor progression and inhibiting the activity of macrophages, dendritic cells, and T-cells. One approach of myeloid-targeted therapies is colony-stimulating factor 1 receptor (CSF-1R) inhibition, leading to a reprogramming of macrophages against glioblastoma cells. In a phase II trial analyzing the efficacy of a CSF-1R inhibitor, patients with recurrent glioblastoma did not meet the primary endpoint of 6-month progression-free survival.⁶ Additionally, a phase Ib/2 trial combining CSF-1R inhibition with temozolomide and radiotherapy was unable to improve overall survival in newly diagnosed patients.⁷ More research is needed to determine why synergistic therapy failed in this latter patient population, and to determine if targeting specific macrophage phenotypes or TAMs directly will improve the prognosis of patients with glioblastoma.
Vaccines

Tumor cells in glioblastoma often mutate to create new antigens that can be recognized as novel epitopes by T-cells. One such mutation affects the epidermal growth factor receptor (EGFR) and is found in around 40% of glioblastomas. Rindopepimut is a 14 amino acid peptide that resembles the most common EGFR mutation found in glioblastomas (EGFRvIII) and is designed to improve survival in EGFRvIII+ patients. The ACT III phase 2 clinical trial demonstrated an initial survival improvement over standard of care treatment, though the ACT IV phase 3 trial failed to produce a similar outcome and was terminated.⁸⁹ Other treatments include dendritic cell–based (DC–based) vaccines, which appear to have promise in early phase I and phase 2 studies. One DC–based vaccine known as DCVax–L progressed to a phase 3 trial before being terminated due to a lack of funding.¹⁰ Vaccines to other novel antigens may work well in glioblastoma due to significant differences in tumor heterogeneity between individuals, though more research is needed.

**Chimeric antigen receptor (CAR) immunotherapy**

CAR T–cell therapy has radically improved the treatment of hematologic cancers. Chimeric antigen receptors are attached to a patient’s T–cells to specifically target tumor cells in individual patients. Despite their impressive efficacy against hematologic cancers, solid glioblastoma tumors remain elusive due to poor tumor infiltration and rapid antigenic mutation.¹¹ EGFRvIII and IL13Ra2–directed CAR T–cells have shown efficacy in early phase 1 and phase 2 trials, yet are currently limited by rapid antigenic mutations that render single antigen–targeting CAR T cells less effective.¹² Other studies are currently being conducted with bispecific CAR T–cells in combination with other therapies to minimize resistance.

**Conclusion**

Although immunotherapy has reshaped the way that many different cancers are treated, glioblastoma remains elusive and seemingly resilient to current immunotherapy candidates. While there is currently not an approved indication for treatment in glioblastoma, research into immunotherapy as a treatment choice is promising and may soon show adequate evidence to treat these patients.

**Resources**


Edited By: Dr. Kristie Fox
Cancer is among the leading causes of death worldwide, accounting for 9.5 million deaths in 2020, or nearly one in six deaths.¹ Cancer screening is an effective preventive measure that can increase cancer incidence and improve mortality. Screenings for breast, cervical, colorectal, and lung cancers are recommended by the US Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS).² The COVID-19 pandemic has led to a sharp decrease in the recommended cancer screening, which is suspected to lead to cancers being diagnosed at a more advanced stage, and a greater increase in the number of avoidable cancer deaths.³

A recent study published in the Journal of the National Comprehensive Cancer Network on February 1, 2022, revealed a large volume of undetected cancer cases related to the pandemic, with some cancer types being more impacted than others.⁵ In this population-based study, Eskander and colleagues utilized the Ontario Cancer Registry (OCR) to identify individuals diagnosed with cancer from September 25, 2016, to September 26, 2020. OCR is a database consisting of all cancers diagnosed in the province since 1964. Eskander and colleagues used segmented negative binomial regression models to examine weekly cancer incidence count and quantify changes in cancer incidence volume trends due to the pandemic.

The patient cohort consisted of 358,487 adult patients diagnosed with cancer and of whom 37,479 were diagnosed during the pandemic. In Ontario, cancers with organized screening programs include breast, cervical, colorectal, and lung cancers. All other cancers were considered non-screening cancers. Researchers discovered that at the start of the pandemic (around the week of March 15, 2020), there was an immediate 34.3% drop in the mean cancer incidence volume compared with pre-pandemic volumes. There was also a slow increase of 1% in volume in each subsequent week until September 26, 2020. Both the immediate drop in incidence and the weekly slow increase were similar for screening cancers and non-screening cancers.

The largest decline in incidence volume at the start of the pandemic were seen for cervical (68.1%), endocrine (63.1%), melanoma (54.6%), and prostate cancers (54.7%). Hepatobiliary and lung cancers were among the cancer types with lowest decline (4.0% and 13.5% respectively).

When compared to pre-pandemic cancer diagnosis rates, Eskander et al. estimated that the pandemic has resulted in 12,601 fewer cancer diagnoses. Additionally, Eskander and colleagues stated that given the similar baseline sociodemographic and clinical characteristics between patients diagnosed with cancer before and during the COVID-19 pandemic, access to diagnostic care during the pandemic was considered equitable, and that no group was disproportionally impacted by COVID-19-related disruptions. The decline in reported cancer incidence was hypothesized to be related to delays in seeking care among patients who wished to avoid an “already overburdened health system.” Eskander and colleagues illustrated the indirect reverberations of the COVID-19 pandemic on cancer incidence in Ontario, Canada.
In the European Union, at least four national population-based cancer registries also reported notable decreases in cancer-diagnosis notifications.\(^6\) Cancer screening programs have been scaled down due to travel restrictions, stay-at-home orders, and redirection of resources to manage the pandemic.\(^7\) The major effect of the pandemic on cancer screening is the growing number of patients who are being diagnosed for the first time with late, incurable stages of cancer.\(^8\)\(^9\)

Media campaigns on television or radio are a great way to increase public awareness of cancer risks and benefits of cancer screening, as well as help restore cancer screening participation rates to levels prior to the pandemic. Pharmacists should increase effort to reach out to the community more proactively and alleviate the concerns of the apparently healthy individuals to return to routine health care. Further effort should be made by healthcare professionals to create outreach programs aimed at groups that may be less likely to seek or complete cancer screening. Patients who have delayed preventative care during the pandemic should be encouraged to discuss age-appropriate cancer screening with their primary care providers as soon as possible. It is imperative that all healthcare professionals work with patients to close the cancer screening gap caused by the COVID-19 pandemic.

References

Edited By: Dr. Cooper Bailey
Opdualag™ is a novel combination immunotherapy consisting of both nivolumab (Opdivo) and relatimab-rmbw approved for the first line treatment of advanced stage melanoma. Opdualag consists of two immune checkpoint inhibitors. Nivolumab is a PD-1 checkpoint inhibitor, while relatimab is a LAG-3 inhibitor and is the first in its class to receive FDA approval.¹ The combination of these medications works to synergize T-cells, a key part in our body’s immune system. Once activated and synergized, these T-cells work to attack and kill cancerous cells. Opdualag consists of 480mg of nivolumab, and 160mg of relatimab-rmbw, given as an IV infusion infused over thirty minutes every four weeks.¹ The single infusion shortens infusion times, as well as decreases preparation and pharmacy time needed to administer the therapy to the patient. A single infusion can also minimize the risk of errors related to administration. The U.S FDA has approved this treatment for Stage III melanomas that are otherwise unable to be removed by surgery, and for Stage IV melanomas, where the disease is considered metastatic and has spread to other parts of the body and organ systems.² It is approved for treatment of adults and pediatric patients twelve years old and older.² This combination treatment was approved for use in early 2022.

According to the NCCN Malignant Melanoma guidelines, first line therapy for advanced melanoma includes an Anti-PD1 monotherapy, such as pembrolizumab (Keytruda) or nivolumab (Opdivo).³ In addition, a combination of ipilimumab (Yervoy) and nivolumab (Opdivo) can be considered, with ipilimumab being an anti- CTLA-4 immunotherapy.³ Thus far, Opdualag has only been compared head to head to Opdivo monotherapy, and not against other first line therapies, in the Relativity-047 trial.⁴ Other head to head comparison studies will be most likely completed in the future. Based on the results of this study, Opdualag is an attractive option for clinicians who would have previously selected nivolumab or pembrolizumab monotherapy or ipilimumab combination therapy.

The Relativity-047 trial showed that patients receiving Opdualag lived an average of 10 months with no disease progression when compared to 4.5 months with patients receiving Opdivo (nivolumab) alone.⁴ While patient’s receiving Opdualag reported more adverse effects overall in comparison to Opdivo, the adverse effects reported were generally well tolerated. The most common side effects reported were pruritus, fatigue, rash, and joint pain.⁴ These side effects were treatment related, and not considered immune related side effects. The study also reported immune related side effects, of which thyroiditis, rash, diarrhea, colitis, and hepatitis were the most common.⁴ These side effects were not reported to cause a discontinuation of therapy and were treated with immune-modulating medications.

The approval of Opdualag proves to be an exciting option for patients with Stage III or Stage IV melanoma, with data showing that it not only prevents disease progression but is overall well tolerated and easier for administration. In upcoming guidelines, Opdualag will potentially be listed as a first line therapy for this patient population, as well as replacing single agent PD-1 inhibitors.
References

Edited by: Dr. Ginger Blackmon
Multiple myeloma (MM) is a hematologic malignancy considered to be incurable. In 2022, an estimated 34,470 new cases will occur in the United States primarily impacting elderly persons.¹ The disease state is characterized by the proliferation of abnormal clonal plasma cells within the bone marrow. Patients frequently present with complications including hypercalcemia, bone lesions and fractures, anemia, and renal impairment.²

First-line therapy for MM most commonly consists of an immunomodulatory drug (iMID), dexamethasone, and a proteasome inhibitor followed by consolidation with an autologous hematopoietic stem cell transplant, if eligible.³ Alternate regimens include additional therapies such as daratumumab that targets CD38. There is a notable lack of options for refractory MM that fails to respond to first-line therapies, or for progression after initial treatment.⁴

Since the pathology of MM arises from the abnormal development of plasma cells after activation by an antigen, an increased focus has been on targeting B-cell activation.² This can be through receptors such as CD3 expressed by T-cells or by newly identified targets such as B-cell maturation antigen (BCMA), expressed on plasma cells. BCMA is expressed primarily by mature B-lymphocytes and is a prognostic marker since its overexpression and activation is associated with progressive MM5. Additionally, BCMA can act as a diagnostic marker since it has been demonstrated to have selective, elevated expression on malignant plasma cells compared to normal plasma cells. Ergo, BCMA is of interest as a potential therapeutic target.⁵ The novel drug teclistamab has been developed as a bi-specific antibody that targets both CD3 and BCMA4. By targeting both, teclistamab induces T-cell activation and lysis of myeloma cells through redirecting CD3+ T-cells to BCMA+ B-cells.⁴

The MajesTEC-1 trial was a phase 1-2, multi-center clinical trial in 165 adult patients with relapsed or refractory MM who had failed at least three lines of prior therapy.⁴ The three lines of therapy must have included an iMID, a proteasome inhibitor, and an anti-CD38 antibody. Patients received teclistamab once weekly at 1.5 mg/kg in 28 day cycles until disease progression, unacceptable toxicity, withdrawal of consent, death, or the end of the study. The primary endpoint of the study was the overall response rate (ORR; defined as partial response [PR] or better). Secondary endpoints included duration of response, percentage of patients with PR or complete response (CR), time until response, median progression-free survival (PFS), median overall survival (OS), rate of achievement of measurable residual disease (MRD), safety, pharmacokinetics, and immunogenicity. The study was sufficiently powered, as they required a sample size of 100 patients to have a power of 85%.

At the follow-up (median of 14.1 months), the ORR was 63%, with 65 (39.4%) patients having a CR or better, and 97 (58.8%) patients having a very good partial response or better. The median time until response was 1.2 months and 44 (26.7%) of patients showed no MRD at the time of response. The median duration of response was 18.4 months. Median PFS was 11.3 months and median OS was 18.3 months, although these numbers are noted to not be mature at this time.
A high number of patients (156 of 165) reported grade 3 or 4 adverse events, with the most common being neutropenia (64.2%), anemia (37%), and thrombocytopenia (21.2%). Most patients (126, 76.4%) experienced an infection, with 74 (44.8%) having grade 3 or 4 infections. Two patients discontinued treatment due to adverse events (a grade 3 pneumonia and grade 4 progressive multifocal leukoencephalopathy [PML], respectively), while 104 (63.0%) patients skipped at least one dose due to adverse effects. Additionally, the majority of patients experienced hypogammaglobulinemia (74.5%) and cytokine release syndrome (72.1%). Of the patients who experienced cytokine release syndrome, only one was grade 3, with all others being grade 1 or 2 in severity. Neurotoxicity occurred in 24 (14.5%) patients, with one grade 4 seizure in a patient with bacterial meningitis while all others were grade 1 or 2. The most common neurotoxicity was headache, occurring in 14 (8.5%) patients. Five (3%) deaths occurred which were attributed by investigators to treatment, including hepatic failure, COVID-19 infection, pneumonia, and PML.

Patients with at least a partial response demonstrated reduced BCMA levels after treatment. Additionally, patients with response to treatment also demonstrated increased levels of several interleukins, higher levels of CD38 and T-cell immunoglobulin, and CD8+ proteins.

In summary, MajesTEC-1 showed that teclistamab treatment can produce a fairly high response rate in a heavily pretreated population. Further, in patients who responded there was an association with increase survival. While it does have a high rate of grade 3 adverse effects, the investigators note that all the ADR were reversible and did not cause significant disruptions in therapy.

Further studies will need to be done comparing teclistamab to other BCMA-targeted therapies such as CAR-T therapy and belantamab mafodotin. These therapies have their own drawbacks that can limit them as treatment options, such as the high cost and intensive selective process for CAR-T, or the ocular toxicities associated with belantamab mafodotin. With this study, teclistamab shows promise as a new treatment option for patients failing multiple first-line therapies.

References

Edited By: Dr. Amber Clemmons
Pancreatic ductal adenocarcinoma is relatively uncommon with a incidence of 8-12 per 100,000 cases every year and a 1-3 % lifetime risk of developing the disease.¹ Despite advances in the diagnosis and treatment of pancreatic ductal adenocarcinoma, the 5-year survival rate of the diagnosed patient is 3-15%.³ The survival rate of the patient is attributed to the late-stage and incurable-stage diagnosis and the additional high tumor chemoresistance.⁴ Discovering this type of cancer at a later stage results in the lack of the ability of treatment to effectively control the spread of the cancer cells to surrounding blood vessels and other organs. When patients are identified with cancer at earlier stages or is determined to be operable, the rate of survival are substantially better.⁵ There is currently a need for prompt diagnosis in an effort to detect the cancer before it reaches advanced stages.

Early detection of pancreatic ductal cancer is considered essential, but there are several challenges.⁶,⁷ Pancreatic ductal adenocarcinoma is relatively uncommon and screening asymptomatic adults is not encouraged. The existing diagnostic methods incur an unacceptably high rate of false-positive findings.⁸ Testing patients who are considered high risk is encouraged due to the reduction of false-positive results. Patients that are considered high risk include individuals with families with an inherited risk, patients with cystic lesions of the pancreas, and patients that are older than the age of 50 that are newly diagnosed with type 2 diabetes.⁹,¹⁰,¹¹ Research to determine these high risk groups has been an important factor to determining who should be screened and the frequency in which screening for pancreatic cancer is recommended.

Established screening protocols and guidelines exist for early detection of patients with cystic lesions. For individuals that are in this high risk group, the screening program used in the United States is the North American National Familial Pancreatic Tumor Registry. The screening programs include cross-sectional imaging and blood tests using tumor markers. Annual imaging by MRI and endoscopic ultrasound are utilized to detect suspicious lesions located on the pancreas. Guidelines for more frequent surveillance is considered for patients that present larger lesions or lesions with worrisome features.¹² Worrisome features include a cyst larger than 3 centimeters, enhanced thickened cyst walls, non-enhanced mural nodules, the main pancreatic duct being 5 to 9 millimeters with characteristic distal glandular atrophy, and lymphadenopathy. Although there are established screening programs and guidelines for detecting cystic lesions, there are no programs established for newly identified high-risk groups such as new-onset diabetes. Several countries are currently investigating efficient procedures to detect pancreatic cancer in this subgroup of high risk individuals.

The use of biomarkers for early detection of pancreatic ductal adenocarcinoma are being investigated to ensure prompt diagnosis for high risk individuals. Several biomarkers are being studied for efficacy and validity of early detection. One biomarker in particular is CA19–9, carbohydrate antigen 19–9, which is currently used in the management of pancreatic ductal adenocarcinoma.¹³ CA19–9, when combined with other factors, proves to be an influential diagnostic tool. In addition to creating biomarkers, research on providing biomarkers to detect this cancer is being produced by various models for collecting data including MRI and CT analysis, abdominal imaging and creation of synthetic biomarkers. The complexity of biomarker discovery for detection of pancreatic cancer involves the lacking sample quantity of pancreatic ductal adenocarcinoma cases and the necessity of collaboration of national and international studies. Overall, early detection of pancreatic cancer is fundamental to preserving a patient’s survival rate and progress in research is vital.
References


Edited by: Dr. Austin Starkey
A Pediatric Oncology Clinical Pharmacist may be considered by some as a highly specialized area of pharmacy practice. However, it might be surprising to learn of its practical skill set applicable to a multitude of clinical areas. Certainly not for the faint of heart, it is a position which offers several opportunities to apply knowledge and skills from various pharmacy capacities. From designing treatment regimens for children, to prescribing, and how to set yourself up for success, I was able to glean some words of wisdom and perspective after peaking behind the curtain with Dr. Jennifer Thackray, PharmD, BCPS, BCPPS of Memorial Sloan Kettering Cancer Center of New York.

Dr. Thackray’s rise to her current position began at a junior college pursuing a biochemistry degree, where around her third or fourth year she discovered a passion for pharmacy. She then attended University of Oklahoma for pharmacy school, then University of North Carolina for her PGY-1 and PGY-2 residencies in pediatrics. During her residencies, she found herself focusing more on oncology as she progressed. After completing her PGY-2, she joined the Memorial Sloan Kettering Cancer Center. Dr. Thackray knew she didn’t want to just stabilize patients and discharge them. She was drawn to direct patient care which allowed for prospective intervention and emerging situations, while still affording her to continue to follow the patient afterwards. With prescribing rights in New York allowing for significant autonomy, she spends half of her day with patients and answering drug information questions for her providers.

When I asked her how she kept up with the ever-changing world of oncology and what must be more so for pediatrics, she offered it could be difficult to counsel patients on the unknowns. Often their patients are receiving single patient drugs, or phase 1 or 2 trial drugs. It is critical to rely on the foundations established in pharmacy school and training. Often, a new drug builds on a foundation of others and counseling points can be assembled from them. Additionally, it is critical for her to continue to invest in her professional development. For those interested in following in Dr. Thackray’s footsteps, she recommends finding an environment where attending conferences and literature review are valued and encouraged to brush up on the rough areas of understanding.

Dr. Thackray offered some suggestions for students. The further you specialize, the less you use the general knowledge. Learn as much as you can, knowing you will hone them during residency. Pathophysiology and pharmacotherapy foundations are the best building blocks to focus on. The one skill set she did not originally think would be as valuable as it is: interdisciplinary communication. This includes using softer skills such as listening, communication which invites discussion, and considering the concerns of others. She finds residents and students are often hesitant or shy about speaking up. The point of these experiences is to bring your valuable perspective and drug knowledge to the team.

Lifelong learners will find a position in clinical pediatric oncology rewarding, as it is high intensity and includes a long term patient following. Leaning on foundations and finding the common thread to follow leads to success. Pediatric Oncology is a dynamic practice which can easily translate to success in a plethora of opportunities pharmacy has to offer. Dr. Thackray has potently demonstrated how practicing at the top of a pharmacist license has priceless benefits to pharmacist, organization, and ultimately the patient.
Polycystic ovarian syndrome (PCOS) is a prevalent endocrine disorder resulting from hormonal imbalances within countless women of reproductive age. Due to chronic hormonal stimulation, there have been concerns regarding the disease state’s association with the risk of developing gynecological cancers. In a 2018 observational study published in *Medical*, a team of researchers based in Taiwan utilized the National Health Insurance Research Database (NHIRD) to view reports of women who had received a new diagnosis of PCOS in an effort to investigate the affiliated incidence of breast, endometrial, and ovarian cancer at a later time.

In order to appropriately interpret the results, it is vital to have information regarding the design and statistical analysis conducted in the study. The study design was a retrospective, cohort study, that aimed to include women between the ages of 15 and 50 who were present in the database between the years of 1998 to 2013. These women were included if they had a valid diagnosis of PCOS based on blood tests for levels of luteinizing hormone, follicle-stimulating hormone, and testosterone. Women were excluded from the study if they already had received a diagnosis of any gynecological cancer before diagnosis of PCOS, or they were to be excluded if they received a cancer diagnosis within one year of being diagnosed for PCOS. Lastly, if an individual withdrew from the insurance program before the index date, they were to be excluded from data analysis.¹ Key outcomes assessed in this study were the development of breast, endometrial, and ovarian cancer. The end-point of the study included the date on which a patient was diagnosed with cancer, withdrew from insurance, or the end of 2013 (the data collection period).¹

With the given criteria for inclusion and key outcomes, 8155 women were ultimately assigned to the PCOS cohort, while 32,620 women without PCOS were in the comparison cohort. Several methods of statistical analysis were used to produce data on incidence of the three major cancer outcomes. Incidence Rate Ratio (IRR) and Hazard Ratio (HR) were used to compare incidence between the different types of cancers, and a Poisson regression model was used to produce 95% confidence intervals of the two groups.¹ Results from the various statistical analyses found an overall 17-fold higher risk of endometrial cancer in more than 8155 Tiwanese women with PCOS than in the women without PCOS.¹ No association was found between breast or ovarian cancer and PCOS. In discussion, the authors describe that the risk of endometrial cancer is believed to be higher because of the prolonged exposure of the endometrium to unopposed estrogen resulting from an anovulatory state.¹ Because of the extended exposure to estrogen, individuals with PCOS can experience endometrial hyperplasia that develops into cancer. Other affiliated risk factors for the development of endometrial cancer in PCOS patients were described as obesity, unopposed long term estrogen use, infertility, never having been pregnant, diabetes mellitus, and hypertension.¹
The publication further reflects on the strengths and weaknesses of the study, which is pivotal to analyze when interpreting the results. The strengths of the study included the large sample size of over 24 million patients, low referral bias, and high follow up compliance due to accessibility of healthcare in Taiwan. Another strength was found to be that diagnosis for the disease states was made by specialists, so there was a significantly reduced chance of error in collecting participant data.¹ A weakness of the study included a general lack of information regarding patient lifestyle habits, social history, and family history. Prevalence was reported to be understated because the data only reflected individuals who sought out medical evaluation. These were flaws associated with data collection design when utilizing a database. Ultimately, one of the biggest problems associated with the study was reflected in the fact that there were actually only a few cases of endometrial cancer noted, which may reduce the sensitivity and positive predictive value.¹ This definitely brings up concerns regarding the validity of the findings.

Currently, endometrial cancer has no definitive cure, yet it remains treatable by a limited number of FDA approved drugs according to the National Cancer Institute. These medications include Dostarlimab-gxly Jemperli, Keytruda, Lenvatinib, Lenvima, Megestrol Acetate, and Pembrolizumab.² Additionally, combination therapy of Carboplatin-Taxol can be used for treatment of endometrial cancers. There is also no existing cure for PCOS, and therapy aims to alleviate symptoms patients may experience. For management of PCOS and further prevention of endometrial cancer, it is recommended that patients currently balance their hormones using contraceptive therapy (combined birth control pills or progesterone only pills) and healthy lifestyle modifications.³ Along with increased physical activity, PCOS patients should consider weight loss through a low calorie diet, for any reduction in weight may help with infertility.³ There are several drugs that may be used to promote pregnancy in women with PCOS, which include Clomiphene, Letrozole, Metformin, and Gonadotropins.³ To aid with symptoms such as hirsutism, doctors may recommend taking Spironolactone, Eflornithine, or consideration of hair removal procedures.³ For any woman struggling with PCOS, forming an individualized plan with a medical provider is vital for maintaining a decent quality of life as well as early assessment of affiliated risks. Ultimately, with early assessment of cancer risks, proactive treatment measures can be considered.

References

Edited By: Dr. Natasha Olson
Rectal cancers are typically reported under the larger group of colorectal cancers, which is the third most common cancer found worldwide.¹ Around 15–20% of colorectal cancers and about 5–10% of rectal cancers are due to DNA mismatch repair deficiency.²³ Normally, during post-replication of DNA, the mismatch repair system works to repair any incorrect base pair matches made during DNA replication. This system is composed of 4 genes: MLH1, MSH1, MSH6 and PMS2. When one of these genes is defective, the mismatch repair system may fail, leading to DNA mutations that can occur in either the somatic cells or the germline. When they occur somatically, cancers, such as rectal cancer, can develop. When they occur in the germline, it may lead to Lynch syndrome, which is also a common factor for some cancers.⁴ People with a family history of cancer should have genetic testing done, especially for those whose family members were diagnosed before 50 years old.⁵

The treatment approach for locally advanced rectal cancer typically consists of chemotherapy followed by radiation therapy, and lastly, resection of the bowel. Even with a complete pathological response of around 25%, some patients prefer not to undergo surgery due to problems with sexual function and defecation post-resection.³⁶ Immunotherapy as an alternative to bowel resection has been explored for treatment of colorectal cancers. A previous study using pembrolizumab, an anti-programmed death 1 (anti-PD1) blockade agent, in metastatic colorectal cancer demonstrated a partial response of 40% (4/10 patients with mismatched repair-deficient). The study showed a partial response in mismatched repair deficiency with an anti-PD1 agent but no response for metastatic colorectal cancer that was mismatched repair-proficient.⁷

The Memorial Sloan Kettering Cancer Center used previous studies exploring PD1 blockades and investigated the response of anti-PD1 immunotherapy in locally advanced rectal cancer for those with a DNA mismatch repair deficiency. The overall design included nine cycles of dostarlimab followed by chemoradiation and then resection; however, if the patient had a complete response from the anti-PD1 immunotherapy and/or chemoradiotherapy, surgery was not required. There were two primary endpoints for this phase II study. One endpoint focused on a 12-month sustained complete response with dostarlimab compared to dostarlimab with surgery (therefore, the pathological complete response). The second end point focused only on the overall response of the neoadjuvant dostarlimab with or without chemoradiotherapy following. This study had only met the second endpoint at the time of publication, and in the future, plans to address the 12-month follow up.⁸

The Memorial Sloan Kettering Cancer Center study had a total of 16 patients that met the criteria to receive dostarlimab treatment. When published, only 12 of the 16 patients had completed all nine cycles of dostarlimab treatment. Of the 12 patients, all had a clinical complete response (100%); which was defined as no residual disease on endoscopic examination and no residual disease on MRI. All 16 patients have since had no disease progression, and 4 of the 12 who completed the dostarlimab treatment have met the 12-month sustained complete response from anti-PD1 treatment alone. Additionally, adverse effects included dermatitis, pruritus, fatigue, and nausea of grade 1 or 2.

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PD-1 BLOCKADE IN MISMATCH REPAIR-DEFICIENT, LOCALLY ADVANCED RECTAL CANCER

BY ALYSSA SANGALANG
PHARM.D CANDIDATE, 2025
Although the study showed a 100% clinical complete response, it did have some limitations, which were addressed. The sample size was 16 with 69% of the patients being white, and only 12% of the patients being black. With colorectal cancer incidence being greater among black patients, having a larger percentage of the black population incorporated into future studies will help lead to more generalizable results of the population. Expanding the study to include multiple study sites may be one possible way that they would be able to obtain a more representative sample of those with mismatched repair-deficient, locally advanced rectal cancer. One possible downside that was not mentioned, is the possibility of patients developing resistance to the anti-PD1 treatment which could lead to disease presence and possible progression. Relapses to therapy have been documented in melanoma patients and other tumors.

Overall, Memorial Sloan Kettering Cancer Center study does show promising outcomes, especially in cancers with mismatch repair-deficits that have not yet metastasized. If consistent among other cancers, it could give patients the alternative of not undergoing surgical procedures that may negatively affect their quality of life.

References

Edited By: Dr. Tahsin Imam