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An Examination of the use of Corticosteroids for Adverse Effects Related to Immunotherapy Treatment in Cancer Patients

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AN EXAMINATION OF THE USE OF CORTICOSTEROIDS FOR ADVERSE EFFECTS RELATED TO IMMUNOTHERAPY TREATMENT IN CANCER PATIENTS

by

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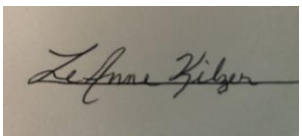
Signature: 

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Abstract

This literature review was carried out after the successful completion of an Objective Structured Clinical Examination (OSCE) and oral defense. The case report involved in the OSCE was not utilized for the literature, an alternative case study was chosen based on a topic of interest expressed by the student. An examination of a current issue in the student's area of practice of Oncology was instead chosen. The subject of the utilization of corticosteroids for adverse effects due to immunotherapy treatment for cancer patients and whether it affects their overall survival was examined. Review of relevant research was completed utilizing the databases of CINAHL and PubMed. Varied combinations of the keywords "immunotherapy, steroid, survival, and cancer" were utilized in the search along with limiting articles that had been published in the last 5 years. Guidelines for the treatment of adverse effects of immunotherapy were examined in the National Comprehensive Cancer Network (NCCN) utilizing the grading criteria from the Common Terminology Criteria for Adverse Events (CTCAE).

The available literature on this subject is mostly retrospective data. A meta-analysis does conclude that the use of corticosteroids for adverse effects of immunotherapy does not affect overall survival. It seems clear that a corticosteroid can be given once immunotherapy has been established for a period of time. However, it remains unclear the appropriate dosing and timing of corticosteroid therapy.

Background

Immunotherapy treatment for cancer traces its origins back to the 1890's with Dr. William B. Coley, who observed cancer remissions in patients with inoperable cancer after patients had life-threatening infections (Sell, 2017). In the early 1900's Coley conducted clinical trials utilizing isolated bacteria into what became known as Coley's toxin, and injecting it into tumors which led to the shrinking of tumors (Sell, 2017). These experiments were unable to be reproduced by fellow scientists and could also have fatal side effects, so this line of treatment was widely discontinued (Sell, 2017). Throughout the rest of the 1900's there was limited success with the trials conducted utilizing different components of immunotherapy, with the exception of viral vaccines. Viral vaccines have undoubtedly been the greatest success of immunotherapy thus far and have been responsible for the prevention of a number of cancers. For instance, Burkitt's Lymphoma, hepatocellular carcinoma, and various cancers related to the human papillomavirus such as cervical and oral cancers, have all had viral vaccines created to help prevent their incidence (Sell, 2017).

The modern era for immunotherapy treatment for cancer seems to have begun in the late 1980's with the monoclonal antibodies, specifically Rituximab which was first approved for use in 1997 (Sell, 2017; FDA, 2020). Shortly after, in the early twenty first century we have seen the advent of immunotherapy agents that are approved for use in more than just one type of cancer, with approvals for multiple types of cancers with immune checkpoint inhibitors. Recently, there has been a lot of media attention, in regard to the potential success of immune checkpoint inhibitors and their possible widespread uses. With the increased use of these agents, the prevalence of adverse effects has increased and led to the need for protocols to manage these effects, which often rely on a form of corticosteroid or another immunosuppressive agent (Pan,

Merl & Lin, 2019). This becomes controversial due to the pathophysiology of the immune checkpoint inhibitor is to increase an immune response by blocking checkpoint proteins and allowing T cell lymphocytes to kill cancer cells. Therefore, it is plausible the administration of a corticosteroid would negate that action of immune therapy by decreasing circulating leukocytes, particularly T lymphocytes (NCI, 2019 and McKay & Cidlowski, 2003). Clinicians are hesitant to use corticosteroids theorizing they may impact the treatment of the immunotherapy thereby negating any gained survival benefits.

The National Comprehensive Cancer Network develops guidelines for the treatment of immune-related side effects based on the severity of the adverse effect. The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 30 leading cancer centers that work together with experts to promote evidence-based-practice by developing clinical guidelines for use by clinicians and patients throughout the world (NCCN, n.d.). Specifically, the section provided in the NCCN for the "Management of Immunotherapy-Related Toxicities" was initially published in 2018, the panel that developed the guideline consists of NCCN Member Institutions along with members of the American Society of Clinical Oncologists (ASCO) and are updated at least annually (NCCN, 2019). This publication allows providers to grade the severity of the side effect and ensure this is done in a standardized method. Providers utilize terminology and descriptions of adverse events put out by the National Cancer Institute (NCI) called the Common Terminology Criteria for Adverse Events (National Institute of Health, n.d.). The NCCN then provides flow charts based on the adverse events the patient is experiencing and provides recommended treatment. The NCCN also publishes clinical practice guidelines for the majority of cancers, supportive care for different side effects, survivorship guidelines, management of immunotherapy-related toxicities as well as others.

The literature review will incorporate aspects of a case study about a male who has received immunotherapy and is suffering from an adverse event related to his treatment. Aspects of this case will be discussed throughout the literature review to relate real world cases to abstract information. Further, the case report will provide some of the details of the case and it will be further analyzed in the literature review.

Case Report

Chief Complaint: Follow-up (kidney cancer): **Date 1/2/2020**

Evaluation and management of metastatic kidney cancer

CURRENT TREATMENT: Nivolumab 480 mg every 28 days

START DATE: 8/1/2019

TODAY: Cycle #11 day 1

Oncology History:

Diagnosis Date: August 2004

Primary Site: right kidney

TNM stage/histology: records not available

Primary treatment: right nephrectomy 3/2004 at Abbott Northwestern

Recurrence 1/2013 in right pleural/pericardium/retroperitoneal nodes

First-line therapy: pazopanib 2/2013 – 3/2013 (discontinued for markedly elevated LFT's)

Second-line therapy: axitinib 4/2013 – 6/2013 (decreased pleural effusion on treatment, discontinued for severe hypertension)

Third-line therapy: temsirolimus x 9 cycles 6/2013 – 9/2013 (discontinued for hepatotoxicity)

Fourth-line therapy: right pleurectomy, wedge resections of lung, resection of diaphragm with repair, ligation of thoracic duct, pericardial window 10/15/2013 (metastatic clear cell neoplasm); right chest wall resection and reconstruction 08/10/2015.

Current sites of disease: right lung nodules, right rib/chest wall metastases

Current treatment: Nivolumab 240 mg every 14 days (changed to monthly on 12/5/2019)

Last cancer imaging: CT CAP 12/4/2019 – Impressions 1. Mild improvement of the metastatic disease in the RIGHT lung. Predominantly stable disease. Destructive rib lesions again noted. These are not significantly changed. Probable LEFT adrenal metastatic disease is stable. LEFT nephrolithiasis is unchanged. 2. Colonic diverticulosis without evidence of diverticulitis. Normal caliber bowel without free air or free fluid.

Chronic problems: right knee pain status post right knee replacement 11/2012

Mediport present: yes

HPI: Patient is an 82-year-old old Caucasian male being followed by Dr. X for recurrent metastatic kidney cancer. He is currently on treatment with Nivolumab every 28 days, was just changed from every 14 days to the every 28-day regimen and has been on this since August. Active areas of disease are lung nodules, right rib/chest wall metastases. He is here today by himself. He is complaining of diarrhea that has been ongoing for 1 month. States frequency of stools is about 5 per day, unable to state an amount, describes stools as watery and brown, denies any blood in bowel movements. Stools are not waking him up at night. Does have urgency throughout the day. Denies accompanying abdominal pain or discomfort. Episodes of diarrhea does not seem to be associated with timing of food or medications.

Review of Systems

Constitutional: Positive for fatigue. Negative for chills and fever.

HEENT: Negative for mouth sores, sore throat, trouble swallowing

Respiratory: Positive for shortness of breath (not above baseline). Negative for chest tightness and cough.

Cardiovascular: Negative for chest pain, leg swelling and palpitations.

Gastrointestinal: Positive for diarrhea. Negative for abdominal distension, abdominal pain, blood in stool, constipation, nausea or vomiting.

Genitourinary: Negative

Musculoskeletal: Positive for arthralgias and myalgias. Negative for back pain.

Skin: Negative for rash

Neurological: negative for dizziness, extremity weakness, headaches, light-headedness and numbness.

Hematological: Negative

Psychiatric/Behavioral: Negative

Past Medical History: HTN, constipation, Type 2 DM, sleep apnea, hearing loss, renal cell carcinoma, obesity, diverticulosis, dyslipidemia, cellulitis, actinic dermatitis

Past Surgical History: Total Knee Arthroplasty (right), Nephrectomy (right), hernia repair, chest wall resection, kidney lithotripsy, eye surgery, cystourethroscopy

Family History: Mother died at age 97 of heart attack, father died at 84 history of stroke; sister and brother have colon cancer history

Allergies: Angiotensin Receptor Blockers, Lipitor (atorvastatin), losartan, lisinopril

Medications: glipizide, labetalol, vitamin D, calcitriol, hydroxyzine HCl, morphine, albuterol inhaler, docusate sodium, gabapentin, amlodipine, hydrochlorothiazide, aspirin, finasteride, tamsulosin, acetaminophen, Symbicort inhaler, zolpidem, ipratropium nasal spray

Objective:

BP 138/71 | P 76 | Temp 97.9 F | SP O2 98% | Wt. 242 lb. | BMI 33

Physical Exam

Constitutional: Alert, oriented. Well groomed, in no apparent distress.

HEENT: Normocephalic and atraumatic. Pink lips. Mucous membranes moist free of sores. Conjunctiva normal. Neck supple.

Cardiovascular: Regular rate and rhythm. Normal heart sounds, S1 normal, S2 normal.

Pulmonary: Effort normal. Normal breath sounds.

Abdominal: Bowel sounds normal. Abdomen soften, nontender.

Musculoskeletal: No edema.

Lymphadenopathy: No cervical adenopathy

Skin: Warm and dry. No rash.

Neurological: No focal deficits present. Alert and oriented, affect normal.

Psychiatric: Attention, mood, speech, behavior, thought content and judgement normal.

Differential diagnosis

Clostridium difficile infection, other stool infection

1. Labs/Imaging: CBC with differential, CMP: **Abnormals** of Creatinine of 1.5, Potassium of 3.4, Chloride 97, Serum Glucose 233, Total Protein 7.7, RBC 4.21, Hemoglobin 10.8, hematocrit 34.8, MCH 25.7, MCHC 31
2. Stool culture, stool for leukocytes, c. difficile GDH and Toxin Antigen; Ova & Parasite Screen (Giardia & Crypto); Calprotectin; lactotransferrin; **Abnormals** of positive for calprotectin and lactoferrin

Assessment:

1. Kidney cancer, primary with metastases from kidney to other site C64.1
2. Diarrhea, unspecified type R19.7; Grade 2
3. Type 2 diabetes mellitus with hyperglycemia, without long-term current use of insulin E11.65

Plan

1. Recurrent metastatic kidney cancer. Had been tolerating nivolumab well. CT scan on 1 month ago showed stable disease with decreased size of sub centimeter nodules. Provider had discussed taking a treatment break versus continuing current therapy, patient opted to continue treatment which was modified to nivolumab 480 mg every 4 weeks. We will hold his dose of nivolumab today due to the diarrhea. He will return in 1 week for cycle #11. Plan for reimaging in March 2020 with CT CAP without contrast.
2. Diarrhea. Obtain stool evaluation to rule out infectious process. After all samples obtained instructed patient he could take loperamide as directed for the next 2-3 days

Follow-up:

1/7/2020: Returned to clinic 5 days later. Therapy continued to be on hold. Per NCCN guidelines patient was started on 60 mg prednisone daily, he will call clinic in 3 days and report diarrhea status. If worsening he is to continue steroids and add infliximab for 3 doses (week 0, 2, 6), consider CT AP with contrast, consider GI consultation and recheck in 1 week. Encouraged him to avoid dairy, acidic or spicy foods.

Summary of Findings

According to the CTCAE, an adverse event is any unintended sign, symptom or disease that is the result of a medical treatment or procedure (NIH, 2017). Adverse events in the CTCAE are measured based on the severity which they refer to as grades, the lowest grade is 1 and the highest grade is a 5 which is death (NIH, 2017). In this case it is important to grade his diarrhea and colitis as these are both adverse events. The most current version of the CTCAE describes diarrhea as a disorder that is characterized by and an increase in the frequency of stool and/or loose or watery bowel movements; and colitis as a disorder characterized by inflammation of the colon (NIH, 2017). The criteria for severity of diarrhea in this case is a grade 2. This is evidenced by the patient's description of diarrhea at an increase in stools by 4-6 times over baseline and this patient described having approximately 5 stools a day, his normal frequency is not noted so we will assume that his normal would be 1 per day (NIH, 2017). The colitis is

slightly more difficult to ascertain as abdominal pain and blood in stools is denied but occasional flank pain is described which could put the patient in grade 1 or grade 2 based on the provider's discretion, in this case due to the occasional abdominal pain the writer would put this patient at a grade 2 (NIH, 2017). The NCCN includes diarrhea and colitis together as symptoms of adverse events, so going to this subsection in the clinical guidelines for "Management of Immune Checkpoint Inhibitor-Related Toxicities" and following the flow chart for management the recommendations are to test the stool for infectious agents and lactoferrin/calprotectin, consider CT CAP if grade 2-4 (recently done), consider GI consultation if grade 2-4; additional management for grade 2 also includes holding immunotherapy, starting prednisone/methylprednisolone at 1-2 mg/kg/day, if no response in 2-3 days then continue steroids and consider adding infliximab or vedolizumab within 2 weeks (NCCN, 2019). This patient had stool evaluated, recently had a CT CAP, had immunotherapy held and was started on 60 mg of prednisone daily with frequent follow up to reassess his symptomology. The patient is about 110 kg, so the dose of 60 mg is closer to 0.5 mg/kg/day which is less than what the NCCN recommends. Though not described explicitly in this case study, we do know that this patient continued on this dose of prednisone for at least 8 weeks along with holding therapy. The question that is posed by this review now is whether his treatment with corticosteroids will affect his overall survival. The concern with corticosteroids is that they would decrease the effect of immune therapy by a number of mechanisms, the most important area of suppression with the immunotherapy is the toxicity the corticosteroid has on T-cells (Petrelli et al, 2020).

Review of Literature

When the body is functioning normally, abnormal cells (precancerous or cancerous) are recognized by the immune system and destroyed. Cancer results when this system is impaired.

There are a number of processes in which cancer cells evade identification and destruction. There are a number of types of immunotherapy, but all are utilizing the body's own immune response to help recognize and destroy those cancer cells. The body has immune checkpoints that help regulate the immune system's response and slow it down or speed it up in response to the presence of a threat (NCI, 2019). When immune checkpoint inhibitors are administered, they block the "off" switch on these immune checkpoints with the results being an increased immune response that allows more identification and destruction of cancer cells (NCI, 2019).

The individual immune checkpoint agents themselves have different mechanisms of action, acting on different receptors, so their side effects even vary individually. Generally, this class of immunotherapy has the potential to cause widespread inflammation throughout a number of organ systems (Milling, Zhang, & Irvine, 2017). This is due to a shortage of regulatory T cells which have a role in protecting the linings of many organs (Milling, Zhang, & Irvine, 2017). Some side effects from the administration of immune checkpoint inhibitors are relatively common, such as rash, diarrhea and fatigue (NCI, 2019). Other effects from these medications are not as common such as pruritis, pneumonitis, hepatitis, hypophysitis, myocarditis, nephritis, and thyroid dysfunction (NCI, 2019).

Corticosteroids have long been used to control inflammation and suppress immune responses. Not all mechanisms of action in the reduction of the inflammatory response is known, but one of the ways they work is to inhibit the recruitment of neutrophils and monocytes (Kufe et al, 2003). Corticosteroids also have a role in activating anti-inflammatory and suppressing pro-inflammatory gene expression through binding with glucocorticoid receptors (Barnes, 2006).

Currently, there is an increase in FDA approved immunotherapies used for various types of cancers, and their use in cancer treatment has rapidly increased. Adverse events often require the use of corticosteroids as treatment. This literature review will explore the use of corticosteroids for immune checkpoint inhibitor adverse events and its effect on patient overall survival. The immune checkpoint inhibitors were a clear choice for evaluation, as there has been a lot of attention around their success. A couple of examples of immune checkpoint inhibitors are anti-Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) and the anti-Programmed Death (PD-1) and anti-Programmed Death Ligand 1 (PDL-1). On utilizing a number of different terms to research the topic within search engines the combination of the following terms yielded the best results related to the topic – "immunotherapy", "steroid", "survival", and "cancer." Primarily the PubMed database was utilized with the key words separated by AND, with a limitation of publication in the last 5 years. The principles of evidenced based practice were also taken into consideration. Particularly, the concept of the Suny Evidence pyramid, which describes different tiers of reliability in medical studies (Suny Downstate Medical Center, 2018. It puts systematic reviews at the highest reliability and top of the pyramid, and in vitro research at the lowest reliability and bottom of the pyramid (Suny Downstate Medical Center, 2018).

The articles chosen for the literature review involved the use of corticosteroids for the adverse effects of immune checkpoint inhibitors and identified a purpose of how the use of corticosteroids impacts patient survival. To best synthesize the findings, four articles were specifically chosen and highlighted in individual article review matrices. Upon close review of these articles with the matrices, it was noted that overall survival was not necessarily their only primary end point. There were a number of different findings among the articles, which makes the literature slightly more challenging when attempting to synthesize the data.

A number of the articles available on the adverse events due to immunotherapy are retrospective data, since the use of immunotherapy is relatively new. Two of the articles evaluated performed retrospective reviews both of which evaluating the use of corticosteroids and its impact on overall survival, yet they both had different findings. One of the articles contends that there is improved overall survival in patients if they have immune related adverse effects in general and then further contends that these results are not altered by whether they received corticosteroids or not (Shafqat, Gourdin, & Sion, 2018). This is a very interesting finding as this was not a circumstance that was hypothesized in the development of the researched topic. The other retrospective review article concentrated on the subset of patients that required corticosteroid use which was about half of their cohort, and came to conclude that high dose steroids (described as greater than 10 mg) for long amounts of time (defined as greater than two weeks) can be associated with poorer survival outcomes (Pan, Merl, & Lin, 2019). It would be interesting if that article had also examined the overall survival of patients who did not have adverse effects to see if they would have come to the same conclusions noted by Shafqat, Gourdin, and Sion (2018). Examining these two articles together, one could possibly presume that survival is dependent on whether the patient has an immune related adverse effect and then on how much and how long steroids were required.

The other two articles examined come from opposite ends of the pyramid described by Suny Downstate Medical Center (2018), with an animal research project and a meta-analysis. While animal research is low on the pyramid of evidence, the information obtained cannot be wholly discounted. The article with animal research really concentrated on examining the pathophysiology of dexamethasone impacts on lymphocyte activation and proliferation while using immune checkpoint inhibitors (Giles et al, 2018). They utilized in vivo and mice in their

studies on the influence of corticosteroids (Giles et al, 2018). Interesting conclusions were made that support the findings of Shafqat, Gourdin, and Sion (2018), the authors found that if cells were treated with corticosteroids prior to starting immunotherapy or early in their treatment course the immune system was unable to mount an appropriate/desired response to the immunotherapy (Giles et al, 2018). One very interesting further finding of this study was that it found the immunosuppressive effects of the corticosteroid were blunted with CTLA-4 drugs but not PD-1 drugs (Giles et al, 2018).

The last article examined was a systematic review/meta-analysis which is the highest tier of evidence in the evidence pyramid (Suny Downstate Medical Center, 2018). The primary end point that the authors were looking for was overall survival (OS) with the secondary endpoint being progression free survival (PFS) which correlated well to the primary topic examined (Petrelli et al, 2020). The authors thoroughly explained their research process along with methodologies utilized, which appears to have high validity. They found that patients who were prescribed steroids for any reason were at an increased risk of death and progression compared to those that were not using steroids (Petrelli et al, 2020). After further analysis was done, the authors recognized a need to differentiate their findings into subgroups and separated steroid use into a cohort, one that needed steroids for immune-related adverse effects and a second cohort that needed it for other reasons such as palliative symptom management (Petrelli et al, 2020). When the data is separated in this manner it showed no detrimental effect on overall survival (Petrelli et al, 2020). They concluded that corticosteroids can be administered without have a detrimental effect on the overall survival of a patient (Petrelli, 2020).

The varied information in the articles described highlights the complexity of the subject manner. The administration of immunosuppressive therapy while attempting to stimulate an

immune response is counterintuitive. There are times when the use of corticosteroids is necessary, for example, when the patient experiences an immune-related adverse event. Based on the information reviewed some patients should not be started on the immunotherapy if they are already on immunosuppressive therapy with a corticosteroid as they would likely not benefit from the effects of the treatment and thus their overall survival would be decreased. If, immunotherapy is their only option available and they are insistent on treatment and their performance status is adequate despite being on immunosuppressive therapy then based on the review, a CTLA-4 may be an option. The CTLA-4 drugs have been shown to blunt some of the effects of the corticosteroid (Giles et al, 2018), However, this information should be used with caution. When patients' immune system has time to mount a response it seems that a short course of steroids seem to have minimal impact on overall survival. The steroid dose and length of time on steroids is not clearly identified with the exception of the one study and could warrant further investigation. One of the most interesting assertions of the articles presented was the increased overall survival of patient who had immune-related adverse effects versus those that did not (Shafqat, Gourdin, & Sion, 2018). That itself could warrant further investigation as a possible prognostic indicator in those receiving immunotherapy.

Much of the data available on the use of corticosteroids for immune-related adverse effects in patients receiving immune checkpoint inhibitors is limited and retrospective. The entire concept of immune-related adverse effects is a newer subject that is rapidly evolving with the continued advancement in the use of immunotherapy in cancer. Guidelines for the management of these effects were only conceptualized in 2018 and are subject to change frequently. With limited clinical trials on adverse effects specifically it is difficult to make recommendations for treatment and have accurate systematic reviews. Systematic reviews are limited as the majority

of information available to review is retrospective data that is not able to differentiate type, dose and duration of corticosteroids used, which the authors readily admit when discussing their intrinsic limitations. More randomized controlled trials are really needed to create heterogenous data that can be more specific to the questions being asked.

Summary:

- Corticosteroids should not be used on patients who are new to using immunotherapy unless well established in the regimen and for the use of immune related adverse effects
- More research is needed, preferably in randomized controlled trials so more controls can be put in place allowing for heterogenous data
- Short courses of corticosteroids do not appear to effect overall survival in cancer patients receiving immunotherapy
- Patients who have immune-related adverse effects have overall better survival
- CTLA-4 drugs may have more ability to offset effects of corticosteroids than PD-1 drugs

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