Southern California CSU DNP Consortium

California State University, Fullerton
California State University, Long Beach
California State University, Los Angeles

IMPROVING NON-ONCOLOGY PROVIDER KNOWLEDGE OF UNIQUE IMMUNOTHERAPY ADVERSE EVENTS

A DOCTORAL PROJECT

Submitted in Partial Fulfillment of the Requirements

For the degree of

DOCTOR OF NURSING PRACTICE

By

Enza Esposito Nguyen

Doctoral Project Committee Approval:

Elizabeth Winokur, PhD, RN, Project Chair
Dana N. Rutledge, PhD, RN, Committee Member

May 2019

ABSTRACT

Among oncology patients, immunotherapy is being used with increasing frequency both as a single agent and in combination with chemotherapy and radiation. Immunotherapy adverse events (AEs) have a unique presentation and are often overlooked or misdiagnosed especially by non-oncology providers. This doctoral project sought to improve non-oncology provider knowledge about management of adverse events from one specific class of immunotherapy, checkpoint inhibitors, and subsequent patient outcomes. Methods included the use of the Promoting Action on Research Implementation in Health Services (PARIHS) model in delivery of tailored micro-teaching sessions to nurses from several hospital units and to emergency physicians with knowledge assessments before and after. Medical records were reviewed to assess patient and clinical outcomes before and after education of these non-oncology providers. There was a significant uptake in knowledge by non-oncology providers regarding checkpoint inhibitor adverse events and their appropriate management. The medical record review revealed important nurse educational gaps that were addressed at the end of the project. However, due to unforeseen problems in the clinical informatics department and issues with the electronic health record, the record review for patient outcomes was not comprehensive.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGMENTS

I would like to thank the Lord my God for giving me the focus and dedication to complete this degree. Dr. Elizabeth Winokur and Dr. Dana Rutledge for their support and mentorship. I appreciate how excited you both were about this project from the very beginning, and how you both became huge champions of this project. I am grateful for shaping me into a better writer, a deeper thinker, and a humble investigator. Dana, I will never look at a table the same way again. Thank you to Dr. Weissmuller and the entire DNP faculty and staff for your support and allowing me to complete this project across the miles after my move to Austin with my family.

A very special thank you to the staff and colleagues at the Center for Cancer Prevention and Treatment at St Joseph Hospital, for your endless support and dedication to this project. There are many physicians, managers, and nurses who appreciated the need for this project and offered their support. My deepest gratitude to Lavinia, Stacey, Colleen, Kathy Berger, and Drs. John Maurice, Ray Casciari, Tim Byun and so many others for always encouraging me, and for always listening with respect and considering my views, my ideas, and suggestions as crazy as they may have been.

Last, but by no means least, I want to thank my husband Tommy for his support and understanding, it has meant so much to me. You have helped me realize so many dreams! I love you. To my children, Fiorenza and Gabriele thank you for being supportive and dealing with mommy's constraints with time. This degree is for you also.

You are both incredible children and I know you both will accomplish all you set your hearts to do. Also, I want to thank my mom and dad who gave me huge amounts of love and encouragement from the day I was born and taught me to love and persevere.

I dedicate this project to the countless cancer patients and their families over my 22-year career that allowed me to enter their lives and gave me the privilege to embark on this personal journey with them and taught me so much along the way.

BACKGROUND

Cancer and its treatment have long posed challenges for the oncology community. That is, how do providers best treat patients and minimize the collateral damage of anti-cancer agents? The last five years have seen a revolution in the targeted treatment of malignancies with immunotherapy agents such as checkpoint inhibitors (CI). This new class of agents includes subclasses such as programmed death-ligand 1 (PD-L1), programmed cell death protein-1 (PD-1), and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), among others. All offer different pathways to destroy cancer cells than did prior therapies (e.g., chemotherapy or radiation) and as a result, have new and complex adverse effect profiles (Gordon et al., 2017; Mistry, Forbes, & Fowler, 2017).

Some of these new immunotherapy agents (e.g., PD-1, CTLA-4) employ the checkpoint receptors within the immune system to support activation or suppression of T cell function (Davies, 2016). Thus, the adverse events or toxicities that result may be a consequence of the up-regulation of various immune effector cells, such as T cells, natural killer cells, and macrophages (Mistry et al., 2017). Consequently, the immune system – so stimulated – not only attacks malignant cells effectively but also causes an auto-immune response, whereby healthy, normal tissues are also attacked (Davies, 2016; Mistry, Forbes, & Fowler, 2017;).

With the administration of immunotherapy, any organ in the body can be affected, making it hard to predict treatment sequelae. Side effects may be difficult to diagnose and manage because they are often only recognized using diagnosis-of-exclusion. For example, a patient being treated with a PD-1 agent may present with increased shortness of breath, tachypnea, and low pulse oximetry reading. The list of potential etiologies for

this clinical triad is long, and includes infection, pneumonia, pulmonary emboli, and heart attack. However, clinicians tuned in to the patient history and knowledgeable about CI agents and aware the patient has received one may also consider immune-mediated pneumonitis. Indeed, pneumonitis and many CI-mediated adverse events are reversible and managed well with high doses of steroids, which is counterintuitive to the work-up and treatment of the symptoms described. Recent reports document patients who have died because adverse events from immunotherapy were not adequately recognized and managed (Davies, 2016; Mistry et al., 2017; Wang et al., 2018).

Fortunately, these new treatments produce durable responses and stable disease in advanced malignancies such as lung cancer, renal cell cancer, and melanoma, thus prolonging life for some patients (Langer et al., 2016; Larkin et al., 2015). Consequently, clinicians are expanding their use to other malignancies and to patients with earlier stages of cancer. A February 2018 search on the National Institutes of Health-sponsored site clinicaltrials.gov utilizing the words ‘cancer’ and ‘immunotherapy’ revealed 1,914 clinical trials of immunotherapy agents that were actively accruing patients in the US and other Western countries; this contrasts the marked increase to 2,535 as of January 2019. It is evident that the number of patients receiving these drugs and potentially experiencing these adverse events is going to continue to increase in the coming years.

Kroschinsky et al. (2017) and Ciccolini, Lucas, Weinstein, and Lacouture (2017) discuss a lack of evidence-based guidelines for the management of these potentially life-threatening complications. In fact, only in October 2017 did the International Association for the Study of Lung Cancer release the first published clinical practice guidelines, followed in February 2018 by those from the National Comprehensive Cancer Network

(NCCN). Up to this point, case studies substantiated the lack of knowledge and awareness by non-oncology providers about CIs and their AEs (Kroschinsky et al., 2017; Mistry et al., 2017). Because these agents are still relatively new, non-oncology providers who care for patients presenting with debilitating and life-threatening side effects are likely to have a limited understanding of the pharmacokinetics of these treatments and no knowledge of these guidelines, impeding appropriate care delivery and adequate management.

Significance

It is critical for clinicians, especially those in non-oncology services such as emergency care, internal medicine, and critical care, to have accurate, up-to-date information on these new therapies, and know how to properly identify immunotherapy-related problems. Some of the less severe but common side effects are dermatologic toxicities in the form of pruritus and rash, which are reported by half of the patients receiving CIs (Davies, 2016). Gastrointestinal toxicities can include abdominal pain, nausea, and diarrhea, which can develop into life-threatening colitis. The risk of intestinal perforation is moderate in patients with colitis from immunotherapy due to tissue damage from autoimmunity (Kroschinsky et al., 2017). Equally life threatening is the development of a cough and shortness of breath that can advance into immune-mediated pneumonitis, which is most common in patients previously treated with surgery and radiation to the lungs as part of their management for lung malignancies (Doyle, 2016).

Improperly treated, any of these adverse events can lead to significant morbidity and even mortality. The prevalence and outcomes of these adverse events have been reported by investigators in many of the trials that led to medication approval. See

Appendix A, Table 1. For example, Larkin et al. (2015) studied the use of nivolumab and ipilimumab alone and in combination and reported the following treatment-related adverse events. Patients receiving nivolumab and ipilimumab alone experienced any grade adverse event, 82.1%, and 95.5%, respectively. When used in combination, adverse events were reported in 95.5% of patients. Similarly, Langer et al. (2016) report grade 2 pneumonitis in 3% of patients receiving chemotherapy and a CI, and grade 3 in 2% of patients. Conversely, patients receiving chemotherapy alone did not experience these serious adverse events (Langer et al., 2016). The rate and frequency of adverse events vary depending on the type and class of immunotherapy agent. Gordon et al. (2016) reported specific adverse events for two classes of CIs in up to 20% of patients. For example, ipilimumab, a CTLA-4 agent, reported the incidence of diarrhea/colitis in 5-16% of patients, whereas, atezolizumab, a PD-L1 inhibitor, diarrhea/colitis incidence was as high as 20%.

Local Context

As of December 2018, at the Center for Cancer Prevention and Treatment (CCPT) at St. Joseph Hospital in Orange, California, there were roughly 110 patients with various cancer diagnoses receiving immunotherapy as part of their treatment. This compares to 50 in February 2018, a 120 % increase in just ten months (V. Green, personal communication, February 04, 2019). At that time, over 80% of clinical trials brought forward for consideration at the CCPT involve immunotherapy (L. Dobrea, personal communication, February 20, 2018). And the number of clinical trials evaluating various new immunotherapy agents, and the combination of existing ones in immunotherapy, were expanding.

Anecdotally, several cancer-center oncologists have reported cases of patients with immune-related adverse events who were admitted through the emergency department and managed on a medical unit, without the notification of the treating oncologist. For example, a case was presented at the multidisciplinary tumor board in May 2017 of a patient admitted with diarrhea and abdominal pain who was on immunotherapy for advanced lung cancer. Several days elapsed before the oncology team was informed. Hospitalists were not aware of the treatment with immunotherapy nor the appropriate management of immune-mediated colitis. Once the oncology team became involved and the patient received the appropriate treatment, the diarrhea resolved.

These reports document a knowledge gap among non-oncology providers and staff at the hospital. On June 2017, a group of clinicians met to develop a plan to address these potentially dangerous gaps. A wallet card to be carried by immunotherapy patients was developed to indicate their specific treatment for cancer; patients were taught to show this to providers when entering the emergency department. Additionally, five in-service sessions were conducted during July and August 2017 for emergency department physicians and nurses. Each session began with a-one page 'pre-in-service' survey with five questions, followed by a brief 15-minute presentation, and a 'post-in-service' survey with the same questions. The survey was administered in English only, and the pre- and post-in-service responses were used to evaluate basic knowledge of immunotherapy, adverse events, and their management. Fifty providers from the emergency care center (14 physicians, 36 nurses/technicians) attended.

One of the questions asked was 'Are you familiar with immunotherapy or checkpoint inhibitors in the treatment of cancer patients?' Pre in-service, 74% of staff

responded ‘no’ (Dobrea & Esposito-Nguyen, 2017) (Figure 1). Following the in-service, the same question was answered with 85% of staff stating ‘yes.’ Similarly, another question asked clinicians in the emergency department ‘Are you familiar with the potential side effects of immunotherapy?’ Pre-in-service, 68% of staff answered ‘no’; post-in-service, 100% of staff answered ‘yes’ to the same question (Dobrea & Esposito-Nguyen, 2017). These responses demonstrate the knowledge gap of these providers. These responses demonstrate the knowledge gap of these providers.

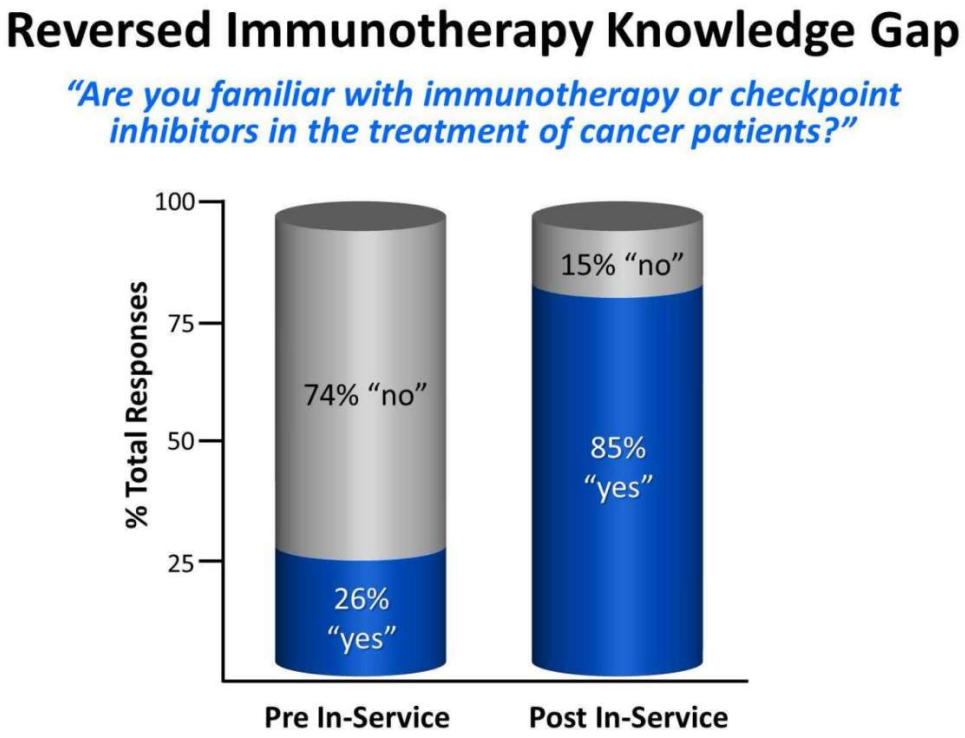


Figure 1. Knowledge gap analysis of emergency department staff at St Joseph Hospital’s emergency department (Dobrea & Esposito-Nguyen, 2017).

Supporting Framework

Implementing clinical practice guidelines involves having strong evidence, a receptive organization, and transformational leaders that can promote knowledge

translation within the health care facility (Rycroft-Malone, 2004). There are several models or frameworks that serve as roadmaps for implementation of evidence-based practice (EBP), such as the Iowa model, Ottawa model for research use, and the Promoting Action on Research Implementation in Health Services (PARIHS) model (Polit & Beck, 2017). Adopting evidence into everyday practice can be very challenging. It is more complex than just presenting the evidence, holding educational meetings, and having providers/staff agreeing to adopt the new practice.

This Doctoral in Nursing Practice (DNP) project utilized the PARIHS model for evidence-based implementation (Harvey & Kitson, 2016) to facilitate the adoption of clinical guidelines for the management of immunotherapy-related adverse events at St Joseph Hospital. Harvey and Kitson (2016) developed this model in the 1990s as a guide to successful implementation (SI) of an innovation (e.g., clinical guidelines); the model takes into account evidence (E) support for the innovation along with qualities of the setting or context (C) where the innovation will be used, and characteristics of the facilitator (F) as shaping successful adoption of guidelines (see Figure 2). More than just a model, it is also a way for clinicians to analyze and evaluate this type of activity arguing that the above-mentioned components are on a continuum from low to high in strength and relevance (Harvey & Kitson, 2016; Kitson et al., 2008).

The core model elements can be further described as dynamic components that affect the likelihood of success in the implementation process. For example, the level and the source of the evidence play an important role in how it is used in patient care (Rycroft-Malone, 2004). Strong evidence is tested and found credible through qualitative and quantitative studies with a strong consensus (Harvey & Kitson, 2016; Rycroft-

Malone, 2004). Additionally, local data collected through gap analysis, surveys, and questionnaires are also important and can be considered in the decision-making process (Rycroft-Malone, 2004). This is the case of the St Joseph Hospital Emergency Department gap analysis described above.

The second element of the framework, context or setting, also has sub-elements such as culture, leadership styles, learning, and priorities (Harvey & Kitson, 2015). There is a continuum from low to high for characteristics that make a setting more or less supportive of evidence-based practice implementation. For instance, settings that are described as 'learning organizations' are champions of change because of a culture of learning and growth (Rycroft-Malone, 2004). These organizations are characterized by "decentralized decision making, an emphasis on the relationship between manager and worker, and a management style that is facilitative rather than ordering" (Rycroft-Malone, 2004, p. 299). This description very closely aligns with the concept of shared governance, which is encouraged at St Joseph Hospital.

The facilitator or facilitators in the PARIHS framework also have sub-elements that are rated from low to high; from novice to experienced. Rycroft-Malone (2004) describes this role as filled by an individual or team who aim at helping others understand and adopt new evidence into practice. Additionally, the facilitator must possess skills, knowledge, esteem, and flexibility to adjust their roles and style to the situation and the needs of the process (Harvey & Kitson, 2015: Rycroft-Malone, 2004).

Reviewing the level of evidence gathered on immunotherapy and the recently published guidelines by several societies, the level of evidence is strong and well-timed (see Appendix A for tables of evidence). As illustrated in the next section, an emergency

department in-service and gathering of anecdotal outcomes for immunotherapy patients, was an important exercise in aligning local context (C), priorities and clinical needs as a way of supporting the proposed change (Harvey & Kitson, 2016). The revised PARIHS model focuses not only on the various dimensions of the evidence, setting or context, and its culture and layers but also on the important role the facilitator(s) have in the implementation and adoption of new guidelines (Harvey & Kitson, 2016).

Improving non-oncology provider knowledge of unique immunotherapy adverse effects is the evidence-based innovation. The context or setting is a community hospital in southern California, St Joseph Hospital. The recipients are the multidisciplinary team of non-oncology physicians, nurses, pharmacists, and other healthcare staff. The DNP scholar assumes the role of facilitator or expert clinician, with the collaboration of a physician champion. The facilitator needs to understand the focus of the clinical problem and identify factors to enable the adoption and application of the innovation utilizing PARIHS as a guide.

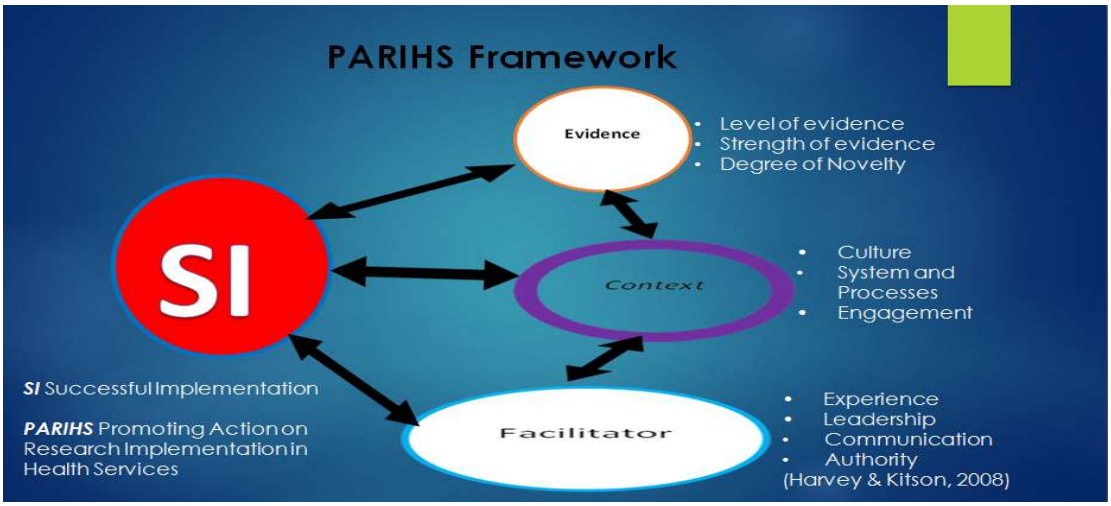


Figure 2. Promoting Action on Research Implementation in Health Services (PARIHS) framework, with a focus on the Context (Adapted from Kitson & Harvey, 2008).

Purpose

The aim of this DNP project was to educate specific non-oncology providers in a community hospital about newly developed clinical guidelines specific to immunotherapy adverse events and evaluate immediate knowledge changes related to identification and management of CI-related adverse events. A subsequent aim was to determine whether patient outcomes related to adverse CI events were handled appropriately once providers at the hospital have received the education.

REVIEW OF LITERATURE

Overview

A systematic appraisal of the literature is the basis for any robust scholarly project, and it served as a solid foundation for this DNP project. The purpose of this project was to educate non-oncology providers in the prompt recognition and management of CI adverse events (AEs) utilizing newly published national guidelines. This review of the literature was divided into the following sections: a) pathophysiology, b) immune-mediated adverse events, c) prevalence of adverse events, d) experience of non-oncology providers, e) use of PARIHS model for guideline implementation, and f) chapter summary.

Pathophysiology

For this section, textbooks on pathophysiology were reviewed and publications relevant to the pathophysiology of auto-immunity were appraised using electronic databases in PubMed and Google Scholar. Key terms utilized included, pathophysiology, auto-immune disease, cancer, and auto-immunity. Reference lists of appraised articles and books were also searched to further identify pertinent publications.

Harnessing the body's immune system to fight cancer and other diseases is a concept that has been studied and utilized for over a century. In a healthy body, regulatory processes by the immune system enable the body to identify abnormal cells that need to be purged or attacked while protecting healthy tissues (Bayer et al., 2017). This surveillance mechanism is well established through the critical role of tumor-reactive cytotoxic CD8 T cells (Tarbell & Egen, 2017). Unfortunately, many tumor cells have developed mechanisms to escape this surveillance with the formation of ligands

(receptor bonds) that interrupt detection by the immune system; these altered cells mimic the appearance of normal cells, and T cell function is suppressed (Davies, 2016; Deel, 2016). For example, one method by which this takes place is by the negative regulation of T-cell function through the cell surface molecules, or checkpoints, CTLA-4 and PD-1 receptors found on tumor cells (Kottschade et al., 2016; Rosenblum, Remedios, & Abbas, 2018).

Therefore, checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4, restore T cell activation by blocking the receptor bond (ligand) responsible for stopping or blocking the immune system (Davies, 2016). By removing the brakes on the immune system, and restoring normal immune function, in particular T cell function, immune cells can better recognize malignant cells and attack the tumor directly (Kottschade et al., 2016; Rosenblum et al., 2018). As a result, a potent anti-tumor response is displayed, as well as the potential for immune-mediated adverse events in various body systems. Moreover, studies in mice models have demonstrated increased auto-immunity when inhibitory pathways such as CTLA-4 and PD-1 have been disrupted in previously healthy subjects (Tarbell & Egen, 2017). This is reflected in the 'collateral damage' seen in many of these adverse events, as healthy body systems are attacked by the newly restored immune system.

Immune-mediated Adverse Events

Blocking the supervision of regulatory checkpoint molecules can result in abnormal immune responses resulting in damage to non-intended targets, such as healthy tissues and body systems (Abdel-Wahab, Shah, & Suarez-Almazor, 2016). Damage has been reported to almost every body system in clinical trials and in case series (Abdel-

Wahab et al., 2016; Larkin, 2015; Ryder et al., 2014). Some of the most common side effects are fatigue and dermatologic toxicities (e.g., pruritus, rash), which are reported by half of the patients receiving check point inhibitors (Davies, 2016; Kroschinsky et al., 2017).

Gastrointestinal (GI) toxicities include abdominal pain, nausea, and diarrhea, which can develop into colitis, and if not managed well, perforation of the bowel. The risk of perforation is higher with colitis in patients receiving immunotherapy due to tissue damage from autoimmunity (Kroschinsky et al., 2017). GI toxicities are most commonly experienced by patients treated with anti-CTLA-4 agents such as ipilimumab (Abdel-Wahab et al., 2016; Larkin, et al., 2015). Equally life threatening is immune-mediated pneumonitis. It is most common in patients extensively treated previously with surgery and radiation to the lungs as part of their management for lung cancer (Doyle, 2016)

Prevalence of Adverse Events

For this section of the literature review, a search was conducted utilizing PubMed, CINAHL, and Google Scholar. Search terms included immunotherapy, checkpoint-inhibitor, guidelines, and adverse event management. Publication between 2011 and 2018 was required, because this new class of therapy was first approved in the US for clinical use in early 2011. All adverse events for this class of medications are graded with the Common Terminology Criteria for Adverse Events (CTCAE) as defined by the National Cancer Institute (NCI). See Table 1 in Appendix A. This uniform grading system allows uniform reporting of adverse events for patients enrolled in clinical trials and has expanded in the last decade into practice (NCI.gov). For example, grade 1 events are considered mild and usually asymptomatic; grade 2 are moderate, usually requiring local

or minimal management; grade 3 are severe and medically significant; and grade 4 are life-threatening and requiring immediate medical care (NCI.gov).

Anti-CTLA-4 Antibodies

Treatments with immunotherapy are increasingly being used in oncology to treat malignancies because of the high proportion and long duration of response rates, along with increased progression-free survival in advanced cancer patients. For example, with the use of ipilimumab, an anti- CTLA-4 antibody, the most common AEs are dermatitis in the form of pruritus and rash, enterocolitis, and endocrinopathies such as hypophysitis and thyroiditis (Fecher, Agarwala, Hodi, & Weber, 2013). Larkin et al. (2015) reported that in patients with advanced melanoma treated with anti- CTLA-antibody, 82% had treatment-related AEs of any grade with 33% of patients experiencing any grade diarrhea. Most notably, patients receiving the anti-CTLA-4 antibody also had a 20% incidence of any grade colitis (Larkin et al., 2017).

Endocrine-related AEs are among the most problematic to patients and most challenging to diagnose and often, the least recognized following treatment with an anti-CLTLA-4 antibody (Ryder, Callahan, Postow, Wolchok, & Fagin, 2014). Hypophysitis leads to acute onset adrenal insufficiency symptoms, accompanied by biochemically low levels, or suppressed levels of serum cortisol, and low levels of adrenocorticotropic hormone (Ryder et al., 2014). In a retrospective review of 211 patients, ipilimumab an anti- CTLA-4 CI, the overall incidence of hypophysitis was 8%, and symptomatic secondary adrenal insufficiency was present in 84% of patients (Ryder et al., 2014). Most affected patients present with headaches and asthenia.

A recent meta-analysis of 81 studies confirmed that skin, endocrine, and GI immune-mediated AEs were the most commonly reported complications with the use of anti-CTLA-4 antibodies (Bertrand, Kostine, Barnetche, Truchetet, & Schaeverbeke, 2015). It is important to note that the incidence of AEs with ipilimumab, an anti- CTLA-4 antibody, was dependent on the dose administered. For instance, the incidence of all-grade AEs was 61% for the 3 mg/kg dose, vs 79% for the 10 mg/kg dose (Bertrand et al., 2015). Autoimmune hypophysitis was the most common endocrine AE, having been reported in 13% of trials; additionally, GI AEs were potentially the most severe immune complications reported (Bertrand et al., 2015). Colitis was reported in 21 patients, with diarrhea and abdominal pain as the most common presenting symptom (Bertrand et al., 2015). See Table 1 in Appendix A.

Anti-PD/PD-L1 Antibodies

Checkpoint inhibitor therapies share some similarities among the different classes. However, there are some striking differences that are important to note. Langer et al. (2016) compared pembrolizumab, an anti-PD-1 antibody, with and without chemotherapy, for the treatment of advanced non-small cell lung (NSCLC) cancer patients in the Keynote-21 trial. The most common AEs reported in the intervention group related to the use of immunotherapy were fatigue (64%) and rash (27%); overall, 22% of patients in the intervention group experiencing presumed immune-mediated adverse events compared to 11% in the chemotherapy alone (control) group (Langer et al., 2016). In contrast to ipilimumab, a CTLA-4 antibody, the PD and PD-L1 agents, pembrolizumab and nivolumab have a very low incidence of GI toxicities (Abdel-Wahab et al., 2016).

There were three cases of any grade pneumonitis in the immunotherapy arm in the Keynote-21 trial, compared to none in the chemotherapy alone arm (Langer et al., 2016). This may be related to the fact that NSCLC patients with advanced disease have been heavily pre-treated with surgery and or radiation to the lungs. In the PACIFIC trial, recently approved for locally advanced NSCLC, durvalumab, an anti- PD-L1 antibody, was tested in combination with radiation therapy (Antonia et al., 2017). In this trial, the most common toxicity leading to discontinuation of the treatment was pneumonitis, with any grade occurrence in 33.9% of durvalumab-treated patients, and 24.8% in the control arm (Antonia et al., 2017).

The combination of these agents for the treatment of advanced melanoma and NSCLC also raises more potentially concerning toxicities. Larkin et al. (2015) reported in their trial looking at nivolumab and ipilimumab, alone or in combination, that the combination of these agents had the highest number of AEs, 95.5%, compared to 82.1% in the nivolumab alone group. Diarrhea and colitis were most commonly experienced in the combination arm and with patients receiving ipilimumab alone (Larkin et al., 2015).

Experience of Non-Oncology Providers

For this section, a literature review was conducted using PubMed, CINAHL, and Google Scholar. Search terms included adverse events, immunotherapy, non-oncology providers, multidisciplinary, and algorithms. Only articles with reports on adult oncology patients were reviewed. Limits on the search included articles between 2012 and 2018. See table of evidence in Appendix A.

These new agents are presenting new challenges for all healthcare providers involved in the care of oncology patients undergoing treatment with CIs because the AEs

are different from those from more traditional treatments, such as chemotherapy. Some AEs may easily be confused for infectious conditions and treated with antibiotics, delaying optimal treatment, contributing to a decline in organ function, and possibly causing untoward results (Kroschinsky et al., 2017; Lomax & McNeil, 2017). As a result, experts are encouraging members of other disciplines, such as dermatology, gastroenterology, emergency medicine, and hospitalists to become familiar with these treatments, the etiology of AEs, and their management (Fecher et al., 2013; Lomax & McNeil, 2017).

Several case reports describe patients admitted through the emergency department or treated in intensive care units with immunotherapy AEs that presented clinical challenges for providers due to lack of knowledge of the pathophysiology and pharmacokinetics of therapies (Kroschinsky et al., 2017; Lomax & McNeil, 2017). See Table 2 in Appendix A. For example, Lomax and McNeil (2017) discuss how patients presenting in the emergency department can start treatment with intravenous steroids for life-threatening presentations if providers are familiar with these clinical presentations. Additionally, the identification of these patients with identification (I.D.) cards for presentation at triage can alert the providers that these patients need management in a distinct way (Lomax & McNeil, 2017).

Because of the new knowledge in the treatment of advanced malignancies, the oncology team will need to coordinate and educate those in other medical specialties and provider groups through educational programs and algorithms. Because of this need, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer

Network (NCCN) have partnered and recently published guidelines for the management of immunotherapy AEs (Brahmer et al., 2018; Fecher et al., 2017).

PARIHS and Guideline Implementation

A literature review was conducted utilizing PubMed, CINAHL, and Google Scholar to review the literature regarding the use of the PARIHS framework and how it has been utilized to adopt new evidence and clinical guidelines in clinical practice. Search terms included PARISH, guideline implementation, implementation, and barriers. The limits of this search were articles that were published between 2010 to 2018. See the table of evidence in Appendix A.

Implementation of new practice guidelines is a complex process perceived by many as involved, time-consuming, and resource intensive. Frequently, new evidence is questioned by clinicians who are accustomed to delivering patient care based on previous knowledge (Udo, Forsman, Jensfelt, & Flink, 2018). Therefore, when a new practice change needs to be studied, understood, and applied, it is important to utilize a framework that has previously been used and learned from its successes and failures. For example, the PARIHS framework (Rycroft-Malone, 2004) has been used to guide implementation of new clinical evidence by demonstrating the relationship between the level of evidence, the individuals involved, and the context (setting) in which the implementation takes place (Udo et al., 2017).

For this reason, when successful implementation (SI) of evidence-based guidelines in the management of cancer-related fatigue (CRF) by nurses in two adult oncology units was carried out, PARIHS was effectively employed as a framework (Tian et al., 2017). In this project, the authors applied SI = Evidence (E) x Context (C) x

Facilitator (F) in the framework, by exploring the sub-elements of these components. For example, C was conceptualized into the multidisciplinary team, the culture of the organization, and degree of support; while E was divided into level of evidence and existing nursing procedures; and finally, F was further seen as considered years of nursing experience, nursing leaders with strong leadership, and champions (Tian et al., 2017). Prior to this project, nurses were not assessing or managing CRF in adult oncology patients. Because of SI, a screening tool and nursing procedures were successfully adopted into daily practice (Tian et al., 2017). Context and its sub-elements were identified by Tian et al. (2017) as important factors in the successful adoption of these guidelines.

A similar project was undertaken in Veterans' Affairs (VA) Hospital spinal cord injury units. Balbale et al. (2015) demonstrated implementation of methicillin-resistant *Staphylococcus aureus* prevention guidelines with the PARIHS framework. In this project, barriers and conduits to implementation were explored to better understand what barriers exist for successful implementation and what strategies would enhance SI. For example, knowledge of providers about new evidence and tailoring these to the organization or context was important to the SI of these guidelines (Balbale et al., 2015). It was important to elicit the input of key recipients, including the multidisciplinary team, and therefore engage them in the implementation process (Balbale et al., 2015). These examples are a sharp contrast to those from a meta-analysis that found that passive learning in the form of printed educational materials (PEM) was not effective at improving patient outcomes or changing provider behavior in the adoption of new clinical knowledge (Grudniewicz et al., 2015).

Summary

The complex nature of the mechanism of action for checkpoint inhibitors, combined with their novel indications, create a multifaceted gap for healthcare providers outside of oncology. This review of the literature highlighted not only the high likelihood of AEs for each class of CI, but also the multi-layered etiology of the AEs. Kroschinsky et al. (2017) summarize this by describing complex cases of patients suffering from immunotherapy AEs in an intensive care unit and show that intensivists navigate attempt to manage acute clinical cases with minimal understanding of their etiology. The evidence reviewed supports the rapidly evolving science and new indications, combinations, and settings for immunotherapeutic agents under study in clinical trials. This evolving context will lead to a rapidly increasing number of patients that will be encountered by specialists and providers outside of oncology.

METHODS

The purpose of this DNP project was to educate non-oncology providers and facilitate the adoption of evidence-based guidelines for management of checkpoint inhibitor-related AEs in a community hospital. Newly published national guidelines were utilized as the evidence (E) to address the management of two checkpoint inhibitor-related AEs, colitis and pneumonitis, in patients receiving this treatment. Prior to implementation of these guidelines, two related quality improvement projects were begun in the hospital. This project was the culmination of three related projects.

During this project, educational in-services were provided to non-oncology nurses and physicians focused on the new guidelines. A knowledge pretest and posttest assessed changes from baseline understanding and chart audits were completed to evaluate success of knowledge dissemination on patient treatment.

Design

The DNP project utilized the PARIHS framework to guide implementation and adoption of AE management guidelines. When health providers attended in-services delivered by the project lead, a pretest was given to assess baseline knowledge of checkpoint inhibitor-related AEs, their identification, and management. Then, a short 7 to 10-minute educational in-service was provided; content focused on the recognition of these AEs (particularly colitis and pneumonitis) and their prompt management according to nationally published guidelines. Following the educational in-service, the same knowledge test was offered to assess knowledge acquisition.

Timeline

With the rapid advent of CIs in the treatment of cancer patients, it was necessary to phase in comprehensive knowledge of these complex treatments and guidelines for management of AEs. Therefore, this DNP project was the culmination of three related projects. The two earlier projects will be labeled as phase one and phase two. Each project had separate health system Institutional Review Board (IRB) reviews. These earlier phases served as preparatory work for the expanded provider teaching component in the DNP project.

Phase one (June and July 2017) introduced CI concepts and basic mechanism of action information to 36 emergency department nurses and physicians. This occurred through educational in-services. The newly developed immunotherapy I.D. card being used in the hospital cancer center (see Appendix B) was introduced to providers during the sessions. Effectiveness of the in-services was measured with a knowledge pretest-posttest.

In an ongoing quality improvement initiative begun in April 2018, phase two aimed to gather (a) numbers of patients admitted to the emergency department or hospital on CIs and (b) numbers of patients treated with CIs, types of adverse events managed by non-oncology providers, and AE treatment (steroids/no steroids; timely/not timely). Data from this phase two project was used to determine patient outcomes as part of the DNP project.

The final phase (DNP project) was evaluation of the targeted education provided for nurses in various non-oncology areas including the emergency care center (ECC), medical-telemetry and oncology units, and the intensive care units. Similar concise,

targeted education was also provided for physicians in the ECC; physician education focused on the newly released management guidelines. A knowledge pretest/posttest was administered to RN and physicians.

Protection of Human Subjects

No provider or patient identifiable information was collected in the course of this project, and as a result, written consent was not sought. For phase one, a certificate from the Human Research Protection Program (HRPP) was obtained from the IRB at St Joseph Hospital in June 2017 (see Appendix C). For phase two, de-identified information was used for the quality improvement data collection on patient outcomes through EHR (electronic health record) review, and a certificate from the health system HRPP was received (see Appendix D). Additionally, the hospital and California State University, Los Angeles (CSULA) IRBs reviewed the DNP project (phase three) prior to initiation and approvals to proceed were also obtained (Appendices E and F). A letter of approval for the project was also obtained from the hospital's Chief Nursing Officer (Appendix G).

Setting

This project was carried out at St Joseph Hospital, a community hospital, in Orange County, California. St Joseph is a 463 bed, not-for-profit hospital with a robust oncology program housed at the Center for Cancer Prevention and Treatment. The hospital is a Magnet-designated facility with about 1000 physicians on staff and over 2,000 nurses employed. The project team consisted of the DNP student (facilitator), the DNP project chair, the manager of the clinical research department, and personnel from clinical informatics.

Measures

Provider Measures

Demographic data collected included the professional designation and the primary unit/specialty of participants. Administered before and immediately after education, a 5-item questionnaire (Appendix H) assessed current knowledge of AEs and their management. Health providers were asked to name checkpoint inhibitor AEs and identify treatment for reversal of AEs.

Patient Measures

Patient data was de-identified. This data was evaluated to determine the following:

a. Number of patients with immune-related adverse events admitted to the hospital or seen in the ECC.
b. Underlying diagnoses of patients receiving immunotherapy/checkpoint inhibitor.
c. Checkpoint inhibitor agents that patients received.
d. Number of hours after ECC arrival until the oncology team was notified.
e. Timing of steroid administration.

Education

Micro-teaching In-services

The unit-based teaching offered to nurses and physicians was administered in micro-teaching sessions, 7 to 10 minutes in length, to small groups of providers (e.g., 5 to 10) during staff meetings or shift huddles. A laptop or a ringed booklet with PowerPoint slides was used for audiovisual aides during these micro-teaching sessions.

This type of short, purposeful, and active educational design draws from adult learning theory (Williams & Da Costa, 2016).

The objectives for the microteaching sessions were to have the learners do the following:

- recognize the mechanism of action of CIs and thus, the etiology of AEs.
- identify differences between traditional oncology treatments and CI
- list common AEs
- identify the role of the non-oncology provider in the management of AEs.

See Appendices H and I for the Power Point slides used for physician and nurse microteaching sessions.

Several in-services sessions were scheduled per area to help cover providers in all shifts. Moreover, the in-service was tailored to either physicians or nurses.

Nursing Grand Rounds

In summer 2018, a nursing grand rounds *Improving non-oncology adoption of immunotherapy adverse events guidelines* was presented at the hospital. See Appendix K for flyer shared with nurses. An announcement from the clinical education department was sent via email to all nurses inviting them to the presentation. The project lead delivered the nursing grand rounds. The objectives for the grand rounds were to discuss background information on checkpoint inhibitors and their mechanism of action, the significance of the non-awareness of immunotherapy AEs (clinical problem), and management of AEs per newly published guidelines. The grand round presentation was 20-minutes in length with 10-minutes allotted for questions and answers. The 5-item knowledge questionnaire was administered to participants before and after the nursing

grand rounds. Nurses were informed at the beginning of the rounds that participation was optional and not mandatory as stated on the questionnaire. About 20 nurses attended the grand rounds.

Procedures

In addition to grand rounds, the project lead presented the education approximately 20 times to physicians and nurses during phase three and final phase of the DNP project. Prior to microteaching sessions, the project lead met with unit managers and charge nurses to discuss dates and times that would best accommodate unit schedules and staff/patient needs. The goal was to reach most of the registered nurses and physicians in the ECC, as well as nurses from the intensive care unit and medical-surgical units throughout the hospital. Attendance was not mandatory but encouraged by the charge nurses and unit managers. A small number of nurses was reached in each non-critical care unit. Nurses from three of six medical-surgical units received the educational micro-teaching. A flyer was posted in each area to announce the educational session (Appendix L). These sessions took place during October to December 2018.

Evaluation

All data from the pre/posttest knowledge questionnaire were analyzed using SPSS (version 24) statistics software. Data was checked for accuracy. Missing data were not imputed. Descriptive statistics were used to describe the demographic characteristics of THOSE who completed the knowledge tests at each time point. Total scores were calculated; and phi coefficients were calculated in order to assess the relationship between baseline and post-education knowledge for each item. Results from the nursing

grand rounds were reported under ‘all RNs’ in the result section. Physician data was reported separately.

Clinical Outcomes

The clinical informatics department was approached in the Spring of 2018 for the need to add a box to check ‘immunotherapy’ in the ‘cancer history’ in the nursing admission section of the EHR. As part of phase two of this project, data from the time period before education (May to September 2018) was compared with that post education (November through December) for number and types of documented patient immunotherapy AEs, notification of the oncology team (yes/no), and whether steroids were administered timely per protocol (yes/no).

When the initial patient data from clinical informatics was shared with the project lead, it was apparent that the ‘immunotherapy’ filtered to identify CI patients was not correctly applied. The project lead worked with the clinical informatics department to rectify these issues. The re-run data demonstrated an insufficient or lower than expected number of patients presenting with immunotherapy AEs.

RESULTS

In this chapter, results include the provider knowledge surveys and clinical patient findings. Knowledge acquisition was described based upon provider role (e.g., physicians; all nurses; nurses from various specialties: ECC, oncology, other). Nurses from grand rounds were included with all other RNs because their work setting was not known.

Knowledge Impact

Between October and December 2018, 73 (66%) nurses and 16 (72%) physicians from the ECC received the in-service, this met our goal to educate most of this critical frontline ECC staff. Additionally, 18 nurses from intensive care, 13 nurses from oncology, 9 nurses from medical-telemetry, and 12 from general surgery participated in the microteaching in-services for inpatient staff. These numbers do not include nurses who attended the Grand Rounds.

Nurses

The results reflect (Table 1) increased knowledge for all nurses (n = 125). For each of the five questions, the percentage of nurses who correctly responded to the item significantly increased at posttest, demonstrating an increase in knowledge ($p < .001$). Baseline nurse knowledge of interventions to reverse checkpoint inhibitor AEs was low prior to the microteaching, 14% correctly responded compared to 96% after education. The question regarding familiarity with newly released guidelines for the management of immunotherapy AEs demonstrated the largest increase in knowledge (see Table 1). Before micro-teaching, 8.5% of nurses answered this question correctly; in contrast, 90.4% answered correctly post-teaching. The final question on the survey asked

participants to list adverse events associated with checkpoint inhibitors. This item increased from a pre-education mean of 0.57 to 3.41 AEs after the microteaching.

Table 1

Responses to Pretest and Posttest Questionnaire by All Nurses

	Pre		Post		
	N = 129		*N* = 125		
	Yes	No	Yes	No	*p*-value
Are you familiar with Immunotherapy as a treatment for cancer?	51.9% (67)	48.1% (62)	96.8% (121)	3.2% (4)	< .0001
Are you familiar with national guidelines for the management of immunotherapy adverse events?	8.5% (11)	91.5% (118)	90.4% (113)	8.0% (10)	< .0001
Are you familiar with the intervention(s) needed to start reversing most immunotherapy adverse events?	14% (18)	86% (111)	96% (120)	3.2% (4)	< .0001
	Pre		Post		
	N = 129		*N* = 125		
	TRUE	FALSE	TRUE	FALSE	*p*-value
Immunotherapy and chemotherapy may be administered simultaneously.	52.7% (68)	45% (58)	89.6 % (112)	9.6% (12)	< .0001
Neutropenic patients who are receiving chemotherapy can be treated with steroids.	49.6 % (64)	48.1% (62)	95.2% (119)	4.0% (5)	< .0001

Tables 2 and 3 show specific groups of nurses by specialty. ECC nurses demonstrated significant increases in knowledge on all items ($p < .0001$). For example, for the question about national guidelines, prior to the in-service 2.7% responded ‘yes’ vs 97.2% afterward. More importantly, the question about being familiar with the intervention to start reversing immunotherapy AEs only received a correct answer 6.8%

before the micro-teaching; afterward, this jumped to 93.2%. Likewise, ECC nurses were able to accurately name an average of 3.77 immunotherapy AEs after instruction compared to 0.52 before.

Table 2

Responses to Pretest and Posttest Questionnaires by ECC Nurses

	Pre *N* = 73		Post *N* = 71		
	Yes	No	Yes	No	*p*-value
Are you familiar with Immunotherapy as a treatment for cancer?	49.3% (36)	50.7% (37)	100% (71)	0	< .0001
Are you familiar with national guidelines for the management of immunotherapy adverse events?	2.7% (2)	97.3% (71)	97.2% (69)	2.8% (2)	< .0001
Are you familiar with the intervention(s) needed to start reversing most immunotherapy adverse events?	6.8% (5)	93.2% (68)	100% (71)	0% (0)	< .0001
	Pre *N* = 73		Post *N* = 71		
	TRUE	FALSE	TRUE	FALSE	*p*-value
Immunotherapy and chemotherapy may be administered simultaneously.	50.7% (36)	49.3% (37)	88.7% (63)	11.3% (8)	< .0001
Neutropenic patients who are receiving chemotherapy can be treated with steroids.	42.5% (31)	57.6% (42)	95.8% (68)	4.3% (3)	< .0001

Table 3 shows that the baseline knowledge of oncology nurses. This was higher than for other nurses. For instance, for question ‘are you familiar with intervention needed to start reversing most immunotherapy adverse events’, prior to the micro-teaching 6.8% of ECC nurses responded ‘yes.’ Conversely, oncology nurses responded ‘yes’ 46.2% prior to micro-teaching. Similarly, for question ‘are you familiar with

national guidelines for the management of immunotherapy adverse events,' 8.5% of all RNs answered 'yes' before teaching, compared to 23.1% of oncology nurses. Like other nurses, after instruction, oncology nurses accurately named more immunotherapy AEs, on average, compared to before: 2.75 after instruction compared to 0.57 before.

Table 3

Responses to Pretest and Posttest Questionnaires by Oncology Nurses

	Pre		Post		
	N = 13		*N* = 12		
	Yes	No	Yes	No	*p*-value
Are you familiar with Immunotherapy as a treatment for cancer?	92.3% (12)	7.7% (1)	91.7% (11)	8.3% (1)	0.953
Are you familiar with national guidelines for the management of immunotherapy adverse events?	23.1% (3)	69.2% (9)	75% (9)	16.7% (2)	0.006
Are you familiar with the intervention(s) needed to start reversing most immunotherapy adverse events?	46.2% (6)	46.2% (6)	83.3% (10)	16.7% (2)	0.083
	Pre		Post		
	N = 13		*N* = 12		
	TRUE	FALSE	TRUE	FALSE	*p*-value
Immunotherapy and chemotherapy may be administered simultaneously.	69.2 % (9)	23.1% (3)	91.7% (11)	8.3% (12)	0.273
Neutropenic patients who are receiving chemotherapy can be treated with steroids.	69.2 % (9)	23.1% (3)	91.7% (11)	8.3% (1)	0.273

Physicians

Table 4 reports the results for the ECC physicians (*n* = 16). At baseline, physician knowledge scores were higher than baseline knowledge for all RNs. For instance, at baseline, for the question 'are you familiar with the intervention needed to start reversing most immunotherapy adverse events,' 21.4% of ECC physicians answered 'yes'

compared to 14% for all RNs and 6.8% for ECC nurses. On only two questions did physicians increase their knowledge significantly post-teaching. One was 'are you familiar with the intervention (s) needed to start reversing most immunotherapy adverse events?' with a significant increase in knowledge following the micro-teaching in-service ($p < .0001$). The other item with a significantly increased proportion of correct responses was being familiar with national guidelines for the reversal and management of CI adverse events ($p = .004$).

Table 4

Responses to Pretest and Posttest Questionnaires by ECC Physicians

	Pre $N = 13$		Post $N = 12$		
	Yes	No	Yes	No	*p*-value
Are you familiar with Immunotherapy as a treatment for cancer?	92.3% (12)	7.7% (1)	91.7% (11)	8.3 % (1)	0.953
Are you familiar with national guidelines for the management of immunotherapy adverse events?	23.1% (3)	69.2 % (9)	75% (9)	16.7% (2)	0.006
Are you familiar with the intervention(s) needed to start reversing most immunotherapy adverse events?	46.2% (6)	46.2% (6)	83.3% (10)	16.7% (2)	0.083
	Pre $N = 13$		Post $N = 12$		
	TRUE	FALSE	TRUE	FALSE	*p*-value
Immunotherapy and chemotherapy may be administered simultaneously.	69.2 % (9)	23.1% (3)	91.7 % (11)	8.3% (12)	0.273
Neutropenic patients who are receiving chemotherapy can be treated with steroids.	69.2 % (9)	23.1% (3)	91.7% (11)	8.3.% (1)	0.273

Patient Outcomes

Reports on patients who received immunotherapy and were admitted to the hospital were evaluated for underlying diagnosis, class of checkpoint inhibitor used for cancer treatment, number of patients with AEs admitted to the hospital or seen in the ECC and use of high dose steroids for management of AEs. Because of reporting issues, initial reports showed duplicate patients, but subsequent reports (Quarter 3 2018) were correct in terms of numbers of patients.

As seen in Table 5, during May through September 2018, three patients were admitted to the project hospital with a CI adverse event. One patient had diarrhea/colitis, the other two presented with pneumonitis. All three patients received adequate doses of steroids and within 24 hours of admission, the oncology team was called. No records were found of patients with potential CI AEs or treated with high doses of steroids during September through December 2018.

Table 5

Patient Outcome Analysis Per Month Reviewed

Month	Immunotherapy Adverse Events reported	Steroid Given	Oncologist Called
May	2	2	2
July	1	1	1
September	0	0	0
November	0	0	0

Related Findings

During the EHR appraisal, it was discovered that ‘immunotherapy’ was only approved to be added to the oncology history (as requested by the project team March

2018) for patients being admitted to the hospital and not those evaluated in the ECC. Therefore, patients seen in the ECC and discharged home could not be identified. This information was not shared by the clinical informatics team until this project was well under way. Because the institution recently merged with a regional health system and the EHR platforms were in the process of changing, no modifications could be made to correct this situation.

Secondly, the EHR review demonstrated that nurses were incorrectly documenting the use of immunotherapy agents. Most errors involved over documentation. For example, patients receiving targeted therapies, such as tyrosine kinase inhibitors (TKIs) were documented as receiving immunotherapy. Two medication classes (targeted therapy and CIs) were being confused by the nurses. There were also cases of under documentation. Patients that were known to have been admitted with CI AEs were missing from the list of immunotherapy patients received from Clinical Informatics list.

DISCUSSION

Increasing use of immunotherapy agents for cancer treatment, along with the expanding indications and combinations of these medications, make provider understanding and management of CI AEs a growing need, especially for non-oncology providers who may care for patients receiving these agents. Known knowledge deficits exist for health providers outside of oncology settings (e.g., emergency departments, intensive care or medical-surgical units); these have caused treatment delays and poor outcomes for patients (Wang et al., 2018). Provider education is needed to ensure safe and effective care of patients receiving these new agents. This project documented the successful effects of brief educational sessions focused on immunotherapy AEs and treatments for hospital nurses and physicians.

Key Findings: Nurses

The pretest administered before education was used as a baseline to determine level of knowledge among providers. Results demonstrated significant knowledge deficits among nurses with correct responses in a range between 9% to 50% to baseline questions. Nurses more than physicians demonstrated limited understanding of the signs and symptoms of adverse events. Interestingly, many nurses and physicians when asked to ‘name some immunotherapy adverse events’ wrote down adverse events associated with chemotherapy. This is congruent with the research which suggests knowledge deficits among providers (Hryniewicki, Wang, Shatsky, & Coyne, 2018; Wang et al., 2018). Post education results (increases in knowledge) for all nurses demonstrate the efficacy of the microteaching session and grand rounds method in knowledge acquisition.

Nurses working on the inpatient oncology unit had better baseline knowledge than "all" nurses: 23% to 90% total scores (indicating percentage of correct responses to all knowledge items). These results indicated that oncology nurses were more familiar with immunotherapy and the management of AEs and thus, had likely been exposed to the recent dissemination of guidelines, perhaps through oncology nursing journals (Gordon et al., 2017; Mistry et al., 2017;). This supports the premise that within the oncology specialty, information about CIs and their AEs is better known and understood. Although oncology nurses are more prepared to identify and manage these issues, these nurses are not involved in patient care during the emergency department visit and may not be involved in care during a hospitalization in a non-oncology unit.

Key Findings: Physicians

Knowledge among emergency physicians was higher than all RNs during baseline assessment with pretest results demonstrating total correct score between 14% to 85% as compared to baseline correct scores of 8% to 52% for all RNs. This could be attributed to a couple of factors. One, there have been recent publications in the emergency department literature regarding checkpoint inhibitor, AEs, and their assessment and management (Hryniewicki et al., 2018; Simmons & Lang, 2017). Secondly, some of these physicians could have attended the introduction educational in-service with introduction of the immunotherapy I.D. cards as part of phase one (summer 2017). Nonetheless, physician knowledge had a statistically significant improvement (p <.0001) when asked if they were familiar with the interventions needed to reverse most immunotherapy adverse events.

Educational Implications

For this doctoral project, the PARIHS model was adapted to focus on the context or setting where new immunotherapy AE guideline education was carried out to evaluate patient outcomes in terms of guideline adoption. St Joseph Hospital is an organization where nurses are encouraged to participate in shared governance, a practice model encouraging accountability and engagement in decisions that affect patient care at every level (Anthony, 2004). Because of this level of engagement, and time constraints on nurses, input was sought from the charge nurses and unit managers regarding best times and locations for an innovative approach to facilitate the educational in-services.

In focusing on the work setting context, the doctoral student tailored the educational offerings in several ways to meet the needs of the health providers. First, it was important to bring the in-service to the staff, instead of holding educational sessions away from the areas where care is delivered. Therefore, the in-service had to be short (no more than 10 minutes). Secondly, the educational audiovisual presentation was loaded onto a compact laptop for portability and allowing the instructor to instruct wherever the need was; also, the presentation slides were printed in a ringed-booklet that was placed at the nurses' station, break room, or board room for use at any time. This format was used for the approximately 20 micro-teaching in-services provided. These strategies help the learners feel valued, involved, and safe to participate (Williams & Da Costa, 2016; Sullivan et al., 2018). This approach, using micro-teaching, emphasized adult style learning, responding to problem solving, and past experiences to stimulate knowledge retention (Williams & Da Costa, 2016). It shows respect for the learner in terms of adaptation to the context of the learning environment (busy hospital unit).

This is in sharp contrast to most hospital-based in-service education which is formalized and presented when staff is not delivering patient care (Teodorczuk, Welfare, Corbett, & Mukaetova-Ladiniska, 2009). Learning programs structured around the needs to the learners are most effective in contrast to more didactic models (Teodorczuk et al., 2009; Williams & Da Costa, 2016). An analysis of post test scores supports the efficacy of this education method. Further, the educational content of offerings was tailored by provider role. Physician education included incidence and response rates, while nurses' education focused on pathophysiology, assessment, and anticipated management of the adverse reaction.

Clinical Outcomes

Although provider knowledge increased, the true measure of the educational intervention is determined by evaluating clinical outcomes (Samuels, McGrath, Fetzer, Mittal, & Bourgoine, 2015). This was to be done by chart audits of patients who received immunotherapy. The review identified several unexpected but important gaps. For example, early EHR reviews revealed that most nurses were over documenting by recording other classes of oncology medications such as targeted therapies (e.g., give an example) or monoclonal antibodies as checkpoint inhibitors. In addition, there were cases of patients on a checkpoint inhibitor with suspected treatment related AEs who lacked important documentation such as medication name and treatment length. These newly identified staff knowledge deficits have been conveyed to the clinical education department of the hospital.

Project Limitations

It is important to mention the limitations associated with this project. One was the short period of time to conduct the project, and inability to educate the entire nursing staff regarding the management of CI AEs. An additional limitation was the inability to educate other specialty physicians such as gastroenterology, cardiology, pulmonary medicine, and endocrinology since doctors within these specialties may need to manage patients with immunotherapy adverse events (Wang et al., 2018).

A limitation out of the control of the project lead was the timing of the project in relation to the hospital's merger with a larger hospital system. Because of the merger, all software and computer updates were placed on hold. This affected the ability of the clinical informatics department to add the 'immunotherapy' query to the past oncology medical history for all patients seeing in the ECC. Clinical informatics was only able to add the query to patients admitted to the hospital. Therefore, this limited the assessment of patient outcomes, because many patients with CI AEs are evaluated in the ECC, some of whom are sent home. This affected the results of the patient outcome review and its implications

Implications for Practice

The PARIHS model proved suitable for this project, particularly in the manner that the micro-teaching in-services were adapted to the audience and setting. It will be important to continue to appraise how micro-teaching could make an impact and even change the way continuing education in healthcare is approached. Today's needs for quick accessible 'pre-packaged' information could be leveraged to make an impact at the bedside.

Although the project was successful in improving provider acquisition of knowledge regarding checkpoint inhibitors and adverse event management, there were gaps identified that require immediate action. These results were shared with managers of the cancer center and infusion suite where patients receive treatment. For example, the gap in knowledge of medication classes by nurses identified during the EHR review (e.g., mistaken identification of other agents as checkpoint inhibitors) was addressed by creation of an oncology medication class table. See Appendix K to review the table, which was distributed to all hospital nurses and Appendix J, which was distributed to all ECC nurses. These tables were developed as soon as the problems were identified; they have been approved by the clinical educational department and managers in the cancer center and in January 2019, were distributed via email to staff with an explanation on how to use the tables when obtaining patient oncology treatment history. The generic table will also be used with new hire orientation.

For future projects, it is recommended that the project team work with the clinical informatics department and information technology regarding upcoming updates or changes that could affect a project's processes, including collection of data. Wood, Migliore, Nasshan, Mirghani, and Contasti (2019) emphasize this step as an essential part of the planning phase to any practice change project. Because of the amount of information contained within an EHR it is difficult to consider that any research, quality improvement, or evidence-based practice project would not use information gathered from the EHR, specifically methods to track patients in real time (Khokhar et al., 2017; Wood et al., 2019). Furthermore, a project lead should find out from other departments

within the site any issues that may be affected by mergers or consolidations; this may be helpful in predicting barriers, and enlisting assistance from stakeholders.

Conclusions

Checkpoint inhibitors are increasingly been used in oncology and at times, their use involves combinations with other modalities. As a result, non-oncology providers will increasingly encounter patients receiving these agents in non-oncology settings throughout the hospital. Brief educational sessions were found effective in increasing nurse and physician knowledge of these immunotherapy agents and their AEs and AE treatments. This project demonstrated the potential of micro-sized targeted education for staff in an era of limited resources and competing time demands. Further implications of this project were the opportunities and challenges of using data from an existing electronic health record. The unexpected findings of educational gaps identified through the patient outcome review gave an opportunity for additional teaching and follow up.

REFERENCES

Abdel-Wahab, N., Shah, M., & Suarez-Almazor, M., E. (2016). Adverse events associated with immune checkpoint blockade in patients with cancer: A systematic review of case reports. *PLOS ONE 11*(7). doi:10.1371/journal.pone.0160221

Anthony, M. (2004). Shared governance models: The theory, practice and evidence. *Online Journal of Issues in Nursing,* 9 (1), 138-153. Retrieved from http://search.ebscohost.com.lib-proxy.fullerton.edu/login.aspx%3fdirect%3dtrue%26db%3daph%26AN%3d16508329%26site%3dehost-live%26scope%3dsiteed from http://search.ebscohost.com.lib-proxy.fullerton.edu/login.aspx%3fdirect%3dtrue%26db%3daph%26AN%3d16508329%26site%3dehost-live%26scope%3dsite

Antonia, S. J., Villegas, A., Daniel, D., Vicente, D., Murakimi, S., Hui, R., . . . Özgűroglu, M. (2017). Durvalumab after chemoradiotherapy in stage III non-small cell lung cancer. *New England Journal of Medicine, 377*(20), 1919-1929. doi:10.1056/NEJMoa1709937

Balbale, S. N., Hill, J. N., Guihan, M., Hogan, T. P., Cameron, K. A., Goldstein, B., & Evans, C. T. (2015). Evaluating implementation of methicillin-resistant Staphylococcus Aureus (MRSA) prevention guidelines in spinal cord injury centers using the PARIHS framework: A mixed methods study. *Implementation Science, 10,* 1-15. doi:10.1186/s13012-015-0318-x

Bayer, V., Amaya, B., Baniewicz, D., Callahan, C., Marsh, L., & McCoy, A. S. (2017). Cancer immunotherapy: An evidence-based overview and implications for practice. *Clinical Journal of Oncology Nursing, 21,* 13-21. doi:10.1188/17.CJON.S2.13-21

Bertrand, A., Kostine, M., Barnetche, T., Truchetet, M. E., & Schaeverbeke, T. (2015). Immune related adverse events associated with anti-CTLA-4 antibodies: Systematic review and meta-analysis. *Bio Med Central Medicine, 13,* 1-14. doi:10.1186/s12916-015-0455-8

Billings, D. M., & Halstead, J A. (2016). *Teaching in nursing: A guide for faculty.* (5th ed.). St. Louis, MO: Elsevier.

Brahmer, J. R., Lacchetti, C., Schneider, B. J., Atkins, M. B., Brassil, K. J., Caterino, J. M., . . . Thompson, J. A. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guidelines. *Journal of Clinical Oncology.* . doi:10.1200/jco.2017.77.6385

Ciccolini, K. L., Lucas, A. S., Weinstein, A., & Lacouture, M. (2017). Advance care provider and nursing approach to assessment and management of immunotherapy-related dermatologic adverse events. *Journal of the Advance Practitioner in Oncology, 8,* 138-145. http://doi.org/10.6004/jadpro.2017.8.2.2.

Davies, M. (2016). How checkpoint inhibitors are changing the treatment pradigm in solid tumors: What advance practitioners in oncology need to know. *Journal of the Advance Practitioner in Oncology, 7*, 498-509. http://doi:10.6004/jadpro.2016.7.5.3

Deel, A. (2016). Nivolumab in metastatic non small cell lung cancer. *Journal of the Advanced Practitioner in Oncology*, *7*(2), 220-225. doi:10.6004/jadpro.2016.7.2.7

Dobrea, L. & Esposito-Nguyen, E. (2017, October). Immunotherapy: Emergency department provider needs assessment survey. Poster presented at 2017 World Lung Meeting, Yokohama, Japan.

Doyle, C. (2016). Managing immune-related toxicities. *The Oncology Nurse,* 9(4), 31-32.

Fecher, L. A., Agarwala, S. S., Hodi, F. S., & Weber, J. S. (2013). Ipilimumab and its toxicities: A multidisciplinary approach. *The Oncologist, 18*, 733-743. doi:.org/10.1634/theoncologist.2012-0483

Gordon, R., Kasler, M. K., Stasi, K., Shames, Y., Errante, M., Ciccolini, K., . . . Fischer-Cartlidge, E. (2017). Checkpoint inhibitors: Common immune-related adverse events and their management. *Clinical Journal of Oncology Nursing, 21*(2), 45-52. doi:10.1188/17.cjon.s2.45-52

Grudniewicz, A., Kealy, R., Rodseth, R. N., Hamid, J., Rudoler, D., & Straus, S. E. (2015). What is the effectiveness of printed educational materials on primary care physician knowledge, behavior, and patient outcomes: A systematic review and meta-analyses. *Implementation Science, 10*, 1-12. doi:10.1186/s13012-015-0347-5

Haanen, J. B.A.G., Carbonnel, F., Robert, C., Kerr, K. M., Peters, S., Larkin, J., & Jordan, K. (2017). ESMO Clinical practice guidelines for diagnosis, treatment and follow. *Annals of Oncology, 28,* 119-142. doi:10.1093/annonc/mdx225.

Harvey, G., & Kitson, A. (2015). Implementing evidence-based practice in healthcare: A facilitation guide. (1st ed.). Oxon, England: Routledge.

Harvey, G., & Kitson, A. (2016). PARIHS revisited: From heuristic to integrated framework for the successful implementation of knowledge into practice. *Implementation Science, 11*(33), 1-3. doi:10.1186/s13012-016-0398-2

Hryniewicki, A. T., Wang, C., Shatsky, R. A., & Coyne, C. J. (2018). Management of immune checkpoint inhibitor toxicities: A review and clinical guidelines for emergency physicians. *The Journal of Emergency Medicine, 55*(4), 489-502. doi: 10.1016/j/jemermed.2018.07.005

IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

International Association for the Study of Lung Cancer. (2017). Immunotherapy Adverse Effect Treatment Resource Guide. https://www.iaslc.org/publications/immunotherapy-adverse-event-treatment-resource-guide. Accessed October 30 2017.

Kitson, A. L., Rycroft-Malone, J., Harvey, G., McCormack, B., Seers, K., & Titchen, A. (2008). Evaluating the successful implementation of evidence into practice PARIHS framework: Theoretical and practical challenges. *Implementation Science, 3*(1), 1-12. doi:10.1186/1748-5908-3-1

Kottschade, L., Brys, A., Peikert, T., Ryder, T., Raffals, L., Brewer, J., …Markovic, S. (2016). A multidisciplinary approach to toxicity management of modern immune checkpoint inhibitors in cancer therapy. *Melanoma Research, 26*, 469-480. doi:10.1097.0000000000000273

Kroschinsky, F., Stölzel, F., von Bonin, S., Beutel, G., Kochanek, M., & Kiehl, M., Schellongowski, P. (2017). New drugs, new toxicities: Severe side effects of modern targeted and immunotherapy of cancer and their management. *Critical Care*, *21*(1), 89. doi:10.1186/s13054-017-1678-1

Langer, C., J., Gadgeel, S., M., Borghaei, H., Papadimitrakopoulou, V., A., Patnaik, A., & Powell, S., F. (2016). Carboplatin and premetrexed with or without pembrolizumab for advanced, non-squamous non-small cell lung cancer: A randomized, phase 2 cohort of the open-label KEYNOTE-021 study. *The Lancet Oncology, 17,* 1497-1508. http://dx.doi.org/10.1016/S1470-2045(16)30498-3

Larkin, J., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Cowey, C. L., Lao, C. D., . . . Wolchok, J. D. (2015). Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *New England Journal of Medicine, 373*(1), 23-34. doi:10.1056/NEJMoa1504030

Lomax, A. J., & McNeil, C. (2017). Acute management of autoimmune toxicity in cancer patients on immunotherapy: Common toxicities and the approach for the emergency physician. *Emergency Medicine Australia, 29*, 245-251. doi:10.1111/1742-6723.12718

Mistry, H., E., Forbes, S., G. & Fowler, N. (2017). Toxicity management: Development of a novel and immune-mediated adverse events algorithm. *Clinical Journal of Oncology Nursing, 21*(2), 53-59. doi:10.1188/17.CJON.S2.53-59.

National Cancer Institute. (2017). Common terminology criteria for adverse events (CTCAE) version 5.0. Retrieved from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

National Comprehensive Cancer Network. (2018). Management of immunotherapy-related toxicities (Version 5.0 2018). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Polit, D. F., & Beck, C., T. (2017). *Nursing research: Generating and assessing evidence for nursing practice*. (10th ed.). Philadelphia, PA: Wolters Kluwer.

Rycroft-Malone, J. (2004). The PARIHS framework for guiding the implementation of evidence-based practice. *Journal of Nursing Care Quality, 19*(4), 297-304.

Ryder, M., Callahan, M., Postow, M. A., Wolchok, J., & Fagin, J. A. (2014). Endocrine-related adverse events following Ipilimumab in patients with advanced melanoma: A comprehensive retrospective review from a single institution. *Endocrinology, 21*, 371-381. doi:10.1530/ERC-13-0499

Rosenblum, M. D., Remedios, K. A., & Abbas, A. K. (2018). Mechanism of human autoimmunity. *The Journal of Clinical Investigation, 125,* 2228-2233. doi:10.1172/JCI178088

Samuels, J. G., Mc Grath, R. J., Fetzer, S. J., Mittal, P., & Bourgoine, D. (2015). Using the electronic health record in nursing research: Challenges and opportunities. *Western Journal of Nursing Research, 37(10)*, 1284-1294. doi:10.1177/0193945915576778

Simmons, D., & Lang, E. (2017). The most recent oncologic emergency: What emergency physicians need to know about the potential complications of immune checkpoint inhibitors. *Cureus, 9*(10), e1774. doi: 10.7759/cureus.1774

Sullivan, S. C., Garner, K. K., Padala, P. R., Padala K. P., Taylor, T, Nabholz, L., … Sullivan, D. H. (2018) 'Bursting' out of the box: Process improvement for interprofessional team in-service education. *Medsurg Nursing, 27(5), 297-299, 322.* Retrieved from http://search.ebscohost.com.lib-proxy.fullerton.edu/login.aspx%3fdirect%3dtrue%26db%3daph%26AN%3d132180600%26site%3dehost-live%26scope%3dsite

Tarbell, K. V., & Egen, J., G. (2018). Breaking self-tolerance during autoimmunity and cancer immunity: Myeloid cells and type I IFN response regulation. *Journal of Leukocyte Biology,* 1-13. doi:10.1002/JLB.3MIR1017-400

Tian, L., Yang, Y., Sui, W., Hu, Y., Huiling, L., Wang, F.,… Tao, M. (2017). Implementation of evidence into practice for cancer-related fatigue management of hospitalized adult patients using the PARIHS framework. *PLoS One, 12,* e0187257. https://doi.org/10.1371/journal.pone.0187257

Udo, C., Forsman, H., Jensfelt, M., & Flink, M. (2018). Research use and evidence-based practice among Swedish medical social workers: A qualitative study. *Clinical Social Work Journal.* doi:10.1007/s10615-018-0653-x.

Wang, D. Y., Salem, Y. E., Cohen, J. V., Chandra, S., Menzer, C., Ye, F., …Johnson, D. B. (2018). Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. *JAMA Oncology*, 4(12), 1721-1728. doi:10.1001/jamaoncol.2018.3923.

APPENDIX A

TABLE OF EVIDENCE

Table 1

Prevalence/Incidence of AEs

Purpose	Design & Variables	Sample & Setting	Measurements	Findings	Conclusions/Notes
The trial examined the use of Durvalumab vs placebo for consolidation therapy in stage III NSCLC pts who did not have disease progression after 2 or more cycles of platinum-based therapy (Antonia et al., 2017).	RTC 2:1 IV -Durvalumab every 2 weeks for 12 months vs. placebo DVs - PFS, OS, RR, AE	713 stage III NSCLC 2:1 ratio to either Durvalumab or placebo after chemoradiation. Pts stratified according to PD-L1 status, smoking Hx, tumor histology. Multi- centered, multi-national study in centers across Asia, Europe and North America.	Assessment for DVs done by blinded independent central review, Q8 weeks for first 12 months, then Q12 weeks. Pts assessed for tumor response using RECIST criteria, version 1.1 Safety, AE per NCI CTCAE version 4.03	Mean PFS 16.8 months with Durvalumab vs 5.6 months placebo PFS benefit observed across all stratified subgroups RR: Durvalumab 28.4% vs 16.0% ($p < .001$). AEs manageable, grade 3 or 4 AE occurred in 29.9% Durvalumab arm vs 26.1%OS: 23.2 months with Durvalumab vs 14.6 AEs similar between groups.	PFS significantly longer with Durvalumab than placebo, OS favors Durvalumab. Responses more durable with IV Note: Pneumonitis most frequent AE with Durvalumab with XRT Importance of combination of CI with XRT
Effect of nivolumab and ipilimumab alone, or in combination in treatment of stages III/IV advanced melanoma pts (Larkin, et al., 2015)	RCT Double blind phase III. 1:1:1 IV drug chosen for treatment (N, I, NI) Randomization stratified per PD-L1	945 previously untreated stages III/ IV advanced melanoma pts at 137 centers in Australia, Europe, Israel,	tumor response - RECIST criteria, version 1.1 at 12 weeks, Q6 weeks x 49.	median PFS 6.9 months N; 11.5 months NI; 2.9 months I + PD-L1 status, median PFS 14	Pts with previously untreated advanced melanoma longer PFS and higher rates of response with N or NI. AE ↑ with NI which needed management with immune

Purpose	Design & Variables	Sample & Setting	Measurements	Findings	Conclusions/Notes
	status; BRAF mutation status; metastatic stage. Treatment until disease progression DV - PFS, AE, OS rates	New Zealand, North America. Stratification per positive, negative or intermediate PD-L1 status; BRAF mutation status negative or positive. Exclusion criteria ECOG ≥ 2 or presence of active brain mets, auto-immune disease or ocular melanoma	Severity of AE NCI CTCAE v4.0 No additional information on specificity or sensitivity.	months in N and NI, 3.9 months in I. AE 82.1% with N, 95.5% with NI, and 86.2% with I	modulator agents such as steroids. offers look at early management of AE Note: article describes rate and management of AEs Most common event diarrhea and colitis in 0.6%, 7.7%, and 8.3% Combination ↑ rate o AE.
To present comprehensive analysis of clinical presentation and experience with endocrine AE in pts with advanced melanoma treated with I or N/I combo (Ryder et al., 2014).	Retrospective analysis 5 trials excluded due to missing data. IV I or N/I vs. control DV: AEs (Hypophysitis, primary thyroid dysfunction, adrenal dysfunction, thyroiditis)	Retrospective analysis of 13 RCTs in pts with advanced melanoma at MSKCC b/t 2007-2013.	Standard quantitative enzymatic or radio immunometric assays (e.g., TSH, T3, T4, ACTH). tests at baseline and during follow up, or as clinically indicated	Incidence of hypothyroidism 6% with I, fatigue, the most common symptom was not quantified. 19 (8% incidence) of Hypophysitis, median onset 4 months. Symptomatic adrenal insufficiency in 16 (84%) Pts 15 (6%) cases of hypothyroidism and 6 (40%) of these were in combo, with male: female 2:4	Hypophysitis was the most common endocrine AE followed by hypothyroidism. Analysis shows strong rationale for monitoring ACTH and cortisol levels in pts receiving immunotherapy, similar to routine TSH being done Note: Great article with data, incidence, management of endocrine AE limitation-retrospective, one institution.

Purpose	Design & Variables	Sample & Setting	Measurements	Findings	Conclusions/Notes
Meta-analysis of incidence and nature of AEs associated with the treatment of advanced cancer with CTLA-4 antibodies (Bertrand et al., 2015).	The CTLA-4 antibodies were I and T, these are the IV Incidence and severity of AEs is the DV reviewed	Meta-analysis and systematic review. 491 articles were reviewed, 81 articles were considered relevant for this review; 57 case review and 24 clinical trials. 20 included I and 4 included T	Severity of AE graded with NCI CTCAE v4.0	Skin AEs affected 44% of patients. GI AEs 35% Autoimmune Hypophysitis was the most common endocrine AE reported in 13% of trials. GI AEs were important and potentially severe immune complications reported. Colitis was reported in 21 patients. Incidence of all-grade AEs dependent on dose of I, 3mg/kg (61%) vs 10mg/kg (79%).	Several specialized centers shared their experience of AEs with other staff to ↑ awareness and introduce early management. Pts with GI AEs including colitis recovered completely. Only 25% of pts with hypophysitis were reported as healed. Awareness of dose and type of CI, important when taking a Hx.
To determine effect of P 200 mg + carboplatin and premetrexed vs carboplatin and premetrexed alone as first-line therapy for pts with advanced non-squamous NSCLC (Langer et al., 2016).	Phase II Study, crossover allowed in patients receiving chemotherapy after radiological confirmed disease progression. IV- P	All pts were treatment naïve, with no prior systemic treatment for stages IIIb/IV and with no targetable EGFR/ ALK. Stratification by tumor PD-L1 (<1%, vs 1% or > 1%) took place. mutations.	Measures at baseline and Q9 weeks x 12 months, Q12 weeks. OR and PFS assessed in intention-to-treat population.	Chemo vs 29% in chemo arm. $p = .0016$. Median PFS 13.0 months for P + chemo vs 8.9 months for chemo alone. No survival differences	Chemo significantly improved number of pts who achieved an objective response. Note: no description of management of AE

Purpose	Design & Variables	Sample & Setting	Measurements	Findings	Conclusions/Notes
	200 mg + carboplatin and P vs carboplatin and P alone DVs OR, PFS, AE	26 academic centers in USA and Taiwan. P 200 mg Q3 weeks for 24 months. Carboplatin and premetrexed Q3 weeks x 4. With premetrexed indefinite maintenance or, 2-drug chemotherapy combination q3 weeks x 4, premetrexed maintenance without pembro	Pts were assessed for tumor response using the RECIST criteria, version 1.1 Safety and A.E. were graded with the NCI CTCAE version 4.03	AE 93% P + chemo vs 90% in chemo group. Most common AEs with P + chemo - hypo/ hyperthyroidism and pneumonitis. Rate of discontinuation due to AE same in both arms, despite > incidences of grade 3+ severity in P+ chemo arm.	
Case presentation to summarize the potential life-threatening complications caused by new cancer agents, including immunotherapy (Kroschinsky et al., 2017).	Anecdotal cases. Great breakdown of each class of new cancer therapy and major side effect profiles; and how to manage them, primarily grade ≥ 3. Example of a clinical algorithm used for PCP in HIV+ patients. This could be extrapolated as an example of how these AE could be managed with a clinical algorithm	Cases of patients exhibiting adverse events, especially in the intensive care unit setting due to article's focus on grade ≥ 3 AEs	NCI CTCAE used as standardized tool for measuring and quantifying grades for AEs	At time of this article, no algorithms for management of immunotherapy AE. Cases illustrate lack of knowledge by non-oncology providers in the management of AEs with CI It is a great article because it was published in a well read and circulated journal, *Critical Care.*	Conclusion: There is still limited knowledge about the pathophysiology of these treatments, and lack of evidence-based guidelines for management of these AE. Lack of understanding by non-oncology staff; and they need support and help from oncology colleagues. Limitation: case review, literature review.

Notes. AE = adverse events; ALK = Anaplastic lymphoma kinase; CI = Checkpoint Inhibitor; CTLA-4 = Cytotoxic T-lymphocyte-associated antigen 4; EGFR = Epidermal growth factor receptor; Hx = History; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = Overall survival; OR = Overall response; PD-L1 = program death ligand1; PCP = Pneumocystis pneumonia; PFS = progression free survival; Pts = Patients; RTC = Randomized controlled trials; RECIST = Response Evaluation Criteria in solid tumors; RR = Response rate; MSKCC = Memorial Sloan-Kettering Cancer Center; XRT = Radiation; T = Tremelimumab.

Table 2

Experience of Non-Oncology Providers and New Guidelines

Purpose	Design and Variables	Sample & Setting	Measurements	Findings	Conclusions/Note
Describes design and implementation of institutional algorithm for management of immune therapy related AE (Mistry, Forbes, & Fowler, 2017).	Data was collected from the published literature about specific toxicities for four major immunotherapy classes. Utilizing this, the institution's experience, and multidisciplinary group consensus, an algorithm was created to manage these adverse events at this institution.	Setting was MD Anderson Cancer Center in Houston, Texas. Two cases reports are described and used to highlight implementation of algorithm in the management of the AE One case had diarrhea and the other pneumonitis.	NCI CTCAE was used as a standardized tool for measuring and quantifying the grade for each AE	2 case studies are used to illustrate need for algorithms. This evidence, along with experience from medical team was used to agree as a team on the algorithms. There was agreement and buy in from multidisciplinary team. Cases illustrate how well the algorithms worked in management of immunotherapy AE at this site	Authors clearly state there are no evidence-based guidelines or algorithms for the management of immunotherapy AE in the literature. Limitation: only case studies, not a meta-analysis. However, highlights the need for these guidelines/ algorithms. Good example of how an institution implemented management algorithms
Article with in-depth description of immunotherapy AE by body system and management guidelines released by the ESMO (Haanen et al., 2017).	Article is broken down into nice sections: general description of AE; combination of immunotherapies; and then AE per body system with accompanied guideline for management. Authors describe development of	The authors all work in oncology centers throughout Europe. Some of the authors have also participated and authored articles on the RCT that led to medication approvals.	The authors used the NCI CTCAE grading criteria for grading of AE which helps in the standardization of AE throughout the literature	Article has great tables, figures and summaries of AE and their management. Presents the new algorithms and management guidelines	The article has great description and data on incidence, rate and management of colitis and pneumonitis which are the 2 AE I want to focus on for my project at St Joes.

Purpose	Design and Variables	Sample & Setting	Measurements	Findings	Conclusions/Note
	guideline per ESMO standard procedures, with summary of recommendations.				
Article has case studies and description and management of immunotherapy AE. It does describe how ED physicians should be knowledgeable about EA and how to manage them in the ED (Lomax & McNeil, 2017).	Case studies and algorithms for the management of immunotherapy AE by body system.	Description on management of AE, and considerations for management these Pts in the ED.	NCI CTCAE is again mentioned to grade immunotherapy AE	Discusses necessity for multidisciplinary team, outside of oncology in the management of these patients and the need to educate them. Need for algorithms to help non-oncology team in the management of AE.	Nice description of the importance and need for ED physicians to understand the pharmacokinetics of immunotherapy and how to manage and assess these patients in the ED. Mentions an immunotherapy card to ID pts. In the ED Therapies being investigated in adjuvant setting, thus increasing the number of eligible pts for tx.
Describes pathophysiology of immunotherapy and AE. Also describes management of AE and necessary involvement of 'body system specialist' to aid in management of system specific (Kottschade et al., 2016).		Mainly describes immunotherapy agent and AE in melanoma patients, however, high number of these issues are seeing in other cancer pts treated with other immunotherapy agents.	NCI CTCAE is used to grade AEs	Importance and need for support from other disease specific specialist such as nephrologists, gastroenterologist, etc. Makes mention twice in article how these patients will increase in number as indications expand.	Many AE can have life-long effects thus stressing importance of collaboration with other specialists

Purpose	Design and Variables	Sample & Setting	Measurements	Findings	Conclusions/Note
Description of immunotherapy AE with a CTLA-4 antibody, I, by body system and use of algorithms to manage AE. Description on the education of multidisciplinary team and patients (Fecher et al., 2013).	Explanation of AE, presentation, timing of onset, and recommendations for management based on algorithms. Suggestions on education of multidisciplinary team, especially non-oncology staff.	Case studies and description of AE by body system.	Description of how algorithms can be used to manage AE.	Assembling and educating a multidisciplinary staff will aid in the prompt and accurate management of these patients.	Mentions immunotherapy ID card; education of multidisciplinary team and algorithms for rapid and accurate management of AE. One of the earliest articles mentioning immunotherapy AE, and implementation of algorithms that were first used by the pharma companies in the RTCs

Notes. AE = Adverse Event; CTLA-4 = Cytotoxic T-lymphocyte-associated antigen 4; ED = emergency department; ESMO = European Society for Medical Oncology; ID = identification; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RTC = randomized controlled trials; Tx = treatment

Table 3

PARIHS and Guideline Implementation

Purpose	Design & Variable	Sample & Setting	Measures	Results	Conclusions/Notes
To implement CRF guidelines in 2 oncology units in China utilizing PARIHS model (Tian et al., 2017).	This project had a 'Pre-implementation' survey and focus group to examine E, C and F in the PARIHS model; there was training for nurses on the level of E and tools for assessment of CRF.	2 oncology wards in a hospital in mainland China. There is data on the surveys pre and post implementation of the EBP using PARIHS. The 2 units were compared to one another	There was an evidence implementation evaluation with surveys. A qualitative approach was used. There is quantitative data on the CRF scale used.	Great discussion on what worked and findings during SI of evidence. Before the EBP medical staff did not assess, grade, or addressed CRF. After EBP a nursing assessment and intervention procedure was developed	Great example on how to carry out an EBP change utilizing PARIHS, great idea on the pre/post implementation surveys. In this article 'high context' is identified as the important factor in successful implementation
To use the PARIHS framework to appraise the implementation of MRSA prevention guidelines in spinal cord injury and spinal disorder patients in the VA system (Balbale et al., 2015).	PARIHS framework was used as basis for the survey questions and semi-structured interviews. Questions investigated characteristics that influence guideline adoption, such as perceived strength of evidence, quality of the context and support for guideline implementation.	24 VA hospitals with a spinal cord injury centers were surveyed, for the second part, 9 VA centers were selected.	First, a cross-sectional survey was administered to all providers in the 24 VA sites (Quantitative) Second phase was semi-structured telephone interviews at 9 VA sites (Qualitative)	Guideline awareness was generally higher among providers who perceived guideline evidence to be high; they also perceived guideline as fully implemented. Individual and system feedback, a Sub-element of C was also discussed as being important. Role of leadership was viewed as important in EBP implementation.	Article is a great example of guideline implementation, discusses elements of E, C, F that need to be considered during implementation.

Purpose	Design & Variable	Sample & Setting	Measures	Results	Conclusions/Notes
Systematic review to assess the effect of PEM on PCP knowledge, behavior, and patient outcomes, compared to no intervention or a different intervention (Grudniewicz et al., 2015).	Systematic review. Studies were looked at with PEM for education and implementation of new guidelines for PCPs.	40 full text articles were included in sample. 8 meta-analysis were conducted with data from 26 studies.	Physician cognition, Physician behavior, patient outcomes were reviewed as far as how PEMs affect these outcomes.	PEMs resulted in significant improvement in outcomes for one of four clinical patient outcomes (physical functioning in patients with multisomatoform disorder).	This review concluded that PEMs do not improve physician cognition, physician behavior, or patient outcomes. Passive evidence dissemination strategies have small affect. This result in relevant to any knowledge translation project, this gives more power a multifaceted framework in guideline implementation.

Notes. C = Context; CRF = Cancer Related Fatigue; EBP = Evidence-Based Practice; PARIHS = Promoting Action on Research Implementation in Health Services; PCP*s* = Primary Care Physicians; PEMs = Printed Educational Materials; VA = Veterans Affair.

APPENDIX B

ST JOSEPH HOSPITAL IMMUNOTHERAPY CARD

Immunotherapy Wallet Card

Front

IMPORTANT INFORMATION

I am receiving or have received
IMMUNOTHERAPY.

Nurse/Doctor
Please read the information on the reverse side of this card.

Oncologist: _____
Contact number: _____

St. Joseph Health
St. Joseph Hospital
The Center for Cancer Prevention and Treatment

Back

ADVICE TO HEALTH CARE PROFESSIONALS

Autoimmune side effects:

- Diarrhea and Colitis
- Hepatotoxicities
- Pneumonitis
- Addison's Disease
- Endocrinopathies
- Neuropathies
- Renal Toxicities
- Skin Rashes

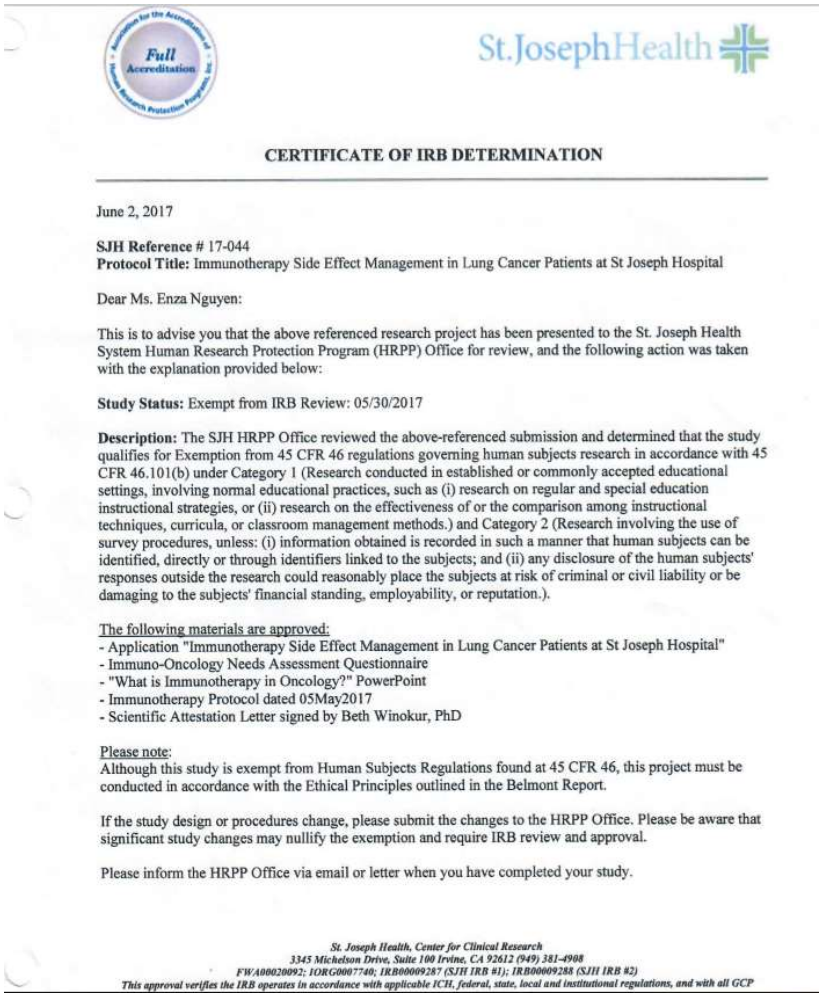
Required blood tests:

- CBC
- Complete Metabolic Panel
- Random Cortisol/ACTH
- Thyroid function test
- If patient has dyspnea, order Chest CT

Steroids are frequently indicated in the management of side effects and may be given.

APPENDIX C

JOSEPH HEALTH SYSTEM HUMAN RESEARCH PROTECTION PROGRAM (HRPP) CERTIFICATE FOR PHASE I



Full Accreditation

St.JosephHealth

CERTIFICATE OF IRB DETERMINATION

June 2, 2017

SJH Reference # 17-044
Protocol Title: Immunotherapy Side Effect Management in Lung Cancer Patients at St Joseph Hospital

Dear Ms. Enza Nguyen:

This is to advise you that the above referenced research project has been presented to the St. Joseph Health System Human Research Protection Program (HRPP) Office for review, and the following action was taken with the explanation provided below:

Study Status: Exempt from IRB Review: 05/30/2017

Description: The SJH HRPP Office reviewed the above-referenced submission and determined that the study qualifies for Exemption from 45 CFR 46 regulations governing human subjects research in accordance with 45 CFR 46.101(b) under Category 1 (Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.) and Category 2 (Research involving the use of survey procedures, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.).

The following materials are approved:
- Application "Immunotherapy Side Effect Management in Lung Cancer Patients at St Joseph Hospital"
- Immuno-Oncology Needs Assessment Questionnaire
- "What is Immunotherapy in Oncology?" PowerPoint
- Immunotherapy Protocol dated 05May2017
- Scientific Attestation Letter signed by Beth Winokur, PhD

Please note:
Although this study is exempt from Human Subjects Regulations found at 45 CFR 46, this project must be conducted in accordance with the Ethical Principles outlined in the Belmont Report.

If the study design or procedures change, please submit the changes to the HRPP Office. Please be aware that significant study changes may nullify the exemption and require IRB review and approval.

Please inform the HRPP Office via email or letter when you have completed your study.

St. Joseph Health, Center for Clinical Research
3345 Michelson Drive, Suite 100 Irvine, CA 92612 (949) 381-4908
FWA00020092; IORG0007740; IRB00009287 (SJH IRB #1); IRB00009288 (SJH IRB #2)
This approval verifies the IRB operates in accordance with applicable ICH, federal, state, local and institutional regulations, and with all GCP

APPENDIX D

JOSEPH HEALTH SYSTEM HUMAN RESEARCH PROTECTION PROGRAM (HRPP) CERTIFICATE FOR PHASE II

St.JosephHealth
Center for Clinical Research

CERTIFICATE OF HRPP DETERMINATION

April 20, 2018

Project Title: Immune Related Adverse Events

Dear Lavinia Dobrea:

This is to advise you that the above referenced project has been presented to the St. Joseph Health System Human Research Protection Program (HRPP) Office for review, and the following action was taken with the explanation provided below:

Determination:
☒The project does not meet the definition of research

Rationale: The SJH HRPP Office reviewed the above-referenced submission and determined that the project activities are limited to quality improvement and does not require SJH IRB Oversight under 45 CFR 46, 21 CFR 56, and SJH Policy due to the following:

- Project does not involve a systematic investigation designed to develop or contribute to generalizable knowledge.
- Project does not seek to test issues that are beyond current science and experience, such as new treatments or untested clinical interventions, or establish scientific evidence.

APPENDIX E

JOSEPH HEALTH SYSTEM HUMAN RESEARCH PROTECTION PROGRAM (HRPP) CERTIFICATE FOR PHASE III

St.JosephHealth

CERTIFICATE OF HRPP DETERMINATION

June 8, 2018

SJH Reference # 18-071 **Protocol Title:** Improving Non-Oncology Provider Adoption of Immunotherapy Adverse Events (AEs) Guidelines

Dear Enza Esposito Nguyen:

This is to advise you that the above referenced research project has been presented to the St. Joseph Health System Human Research Protection Program (HRPP) Office for review, and the following action was taken:

Study Status: Exempt from IRB Review: 06/8/2018
Description: The SJH HRPP Office reviewed the above-referenced submission and determined that the study qualifies for Exemption from 45 CFR 46 regulations governing human subjects research in accordance with 45 CFR 46.101(b) under exemption categories 1 (Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods), 2 (Research involving the use of educational tests, survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation), and 4 (Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are publicly available or the information is recorded by the investigator in such a manner that the subjects cannot be identified directly or through identifiers linked to the subjects.)
Co-Investigators/Research staff approved: Elizabeth Winokur

The following documents were reviewed:
Scientific Attestation (Dana Rutledge)
Letter of Support (Katie Skelton)
Research Intake Form
Application for IRB Exemption signed 6/7/2018
Protocol - Immunotherapy dated 22May2018
Data Collection Tool – ImmunoSJOexcel
Immunotherapy Adverse Events Questionnaire
Proposal Defense PowerPoint
CV: Enza Esposito Nguyen, Elizabeth Winokur

Please note: Although this study is exempt from Human Subjects Regulations found at 45 CFR 46, this project must be conducted in accordance with the Ethical Principles outlined in the Belmont Report.

If the study design or procedures change, please submit the changes to the HRPP Office at HRPP@stjoe.org. Please be aware that significant study changes may nullify the exemption and require IRB review and approval.
Please inform the HRPP Office via email or letter when you have completed your study.

APPENDIX F

CALIFORNIA STATE UNIVERSITY, LOS ANGELES INSTITUTIONAL REVIEW BOARD (IRB)

Office Memorandum

DATE:	September 12, 2018
TO:	Elizabeth Winokur, PhD, RN
FROM:	California State University, Los Angeles (Cal State LA) IRB
PROJECT TITLE:	[1286503-1] Improving Non Oncology Provider Adoption of Immunotherapy Adverse Events (AEs) Guidelines
REFERENCE #:	17-237X
SUBMISSION TYPE:	New Project
ACTION:	DETERMINATION OF EXEMPT STATUS
DECISION DATE:	September 12, 2018
REVIEW CATEGORY:	Exemption category # *2*

Thank you for your submission of New Project materials for this project. The California State University, Los Angeles (Cal State LA) IRB has determined that this project is EXEMPT FROM IRB REVIEW according to federal regulations.

We will retain a copy of this correspondence within our records.

IF ANY CHANGES ARE MADE TO THE METHODS AND PROCEDURES DESCRIBED IN THIS PROTOCOL, YOU MUST SUBMIT ANOTHER APPLICATION SO THAT THE PROJECT MAY BE RE-EVALUATED FOR EXEMPTION FROM IRB REVIEW.

If you have any questions, please contact Elia Amaro at irb@calstatela.edu or irb@calstatela.edu. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within California State University, Los Angeles (Cal State LA) IRB's records.

APPENDIX G

LETTER OF APPROVAL FROM ST JOSEPH HOSPITAL'S CHIEF NURSING OFFICER

St.JosephHealth
St. Joseph Hospital
A member of the St.Joseph Hoag Health alliance

May 16, 2018

St Joseph Health System

Institutional Review Board

This letter documents my strong support for the proposed study *Improving Non-Oncology Provider Adoption of Immunotherapy Adverse Events Guidelines* by Enza Esposito-Nguyen, the nurse leading this quality improvement project. The project's purpose reflects the Magnet-culture at St. Joseph Hospital in terms of identifying a clinical problem or gap, and utilizing evidence based guidelines to meet the clinical need. Adoption of these new guidelines will ensure that our oncology patients are managed more effectively and safely by our multidisciplinary team. Therefore, this will lead to better patient outcomes and shorter length of stay.

I lend my full support for this project for Enza's Doctor of Nursing Practice project with Dr. Elizabeth Winokur as her chair and team lead.

Sincerely,

Katie Skelton

Katie Skelton, RN, MBA, NEA-BC
Vice President Patient Care Services
Chief Nursing Officer

MAGNET RECOGNIZED
1100 West Stewart Drive • Orange, CA 92868
T: (714) 633-9111

APPENDIX H

IMMUNOTHERAPY ADVERSE EVENTS (AES) GUIDELINES IN-SERVICE QUESTIONNAIRE

Your participation and completion of this questionnaire is voluntary. By completing the questionnaire, you are consenting to participation.)

1. Are you a: physician ☐ Nurse ☐ NP/PA ☐ Other _____
2. Are you familiar with Immunotherapy as a treatment for cancer?

   Yes ☐ No ☐

3. Can you name some immunotherapy adverse events or side effects?

   _____ _____ _____

   _____ _____ _____

4. Are you familiar with national guidelines for the management of immunotherapy adverse events?

   Yes ☐ No ☐

5. Are you familiar with the intervention(s) needed to start reversing most immunotherapy adverse events?

   Yes ☐ No ☐

6. Immunotherapy and chemotherapy may be administered simultaneously

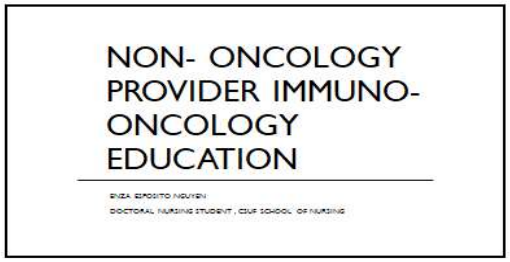
   True ☐ False ☐

7. Neutropenic patients who are receiving chemotherapy can be treated with steroids

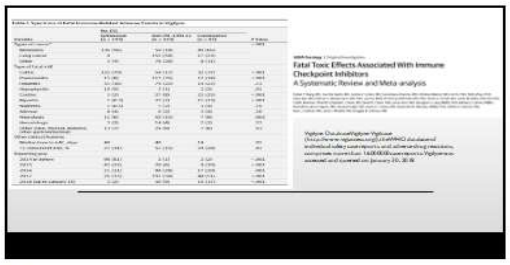
   True ☐ False ☐

APPENDIX I

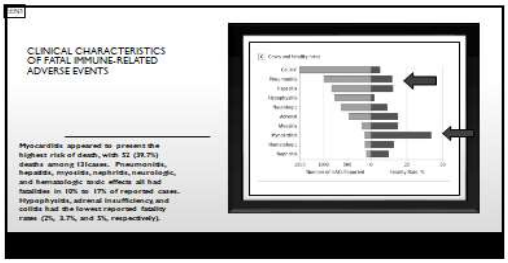
EMERGENCY DEPARTMENT PHYSICIAN MICROTEACHING SLIDES



1



2

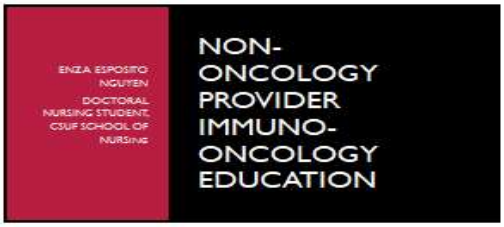


3

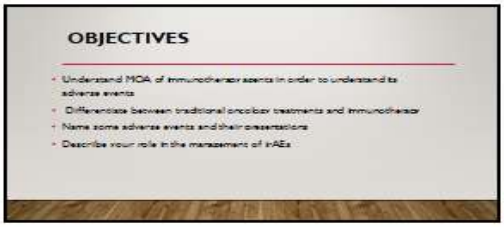
4

APPENDIX J

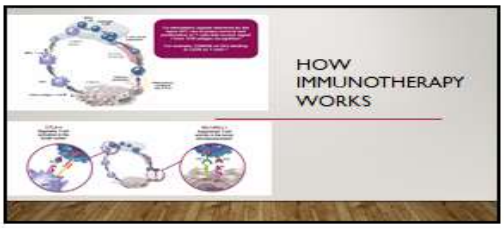
NURSING STAFF MICROTEACHING SLIDES



1

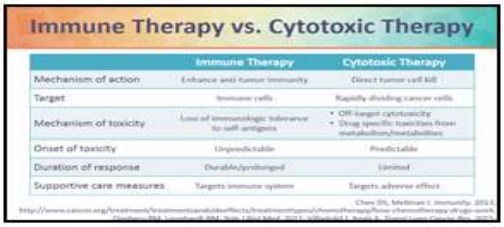


2

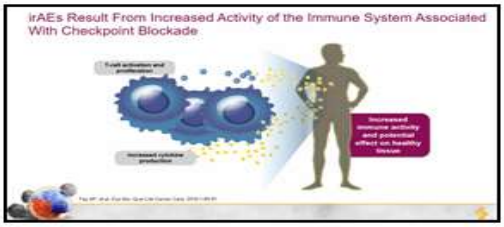


3

4



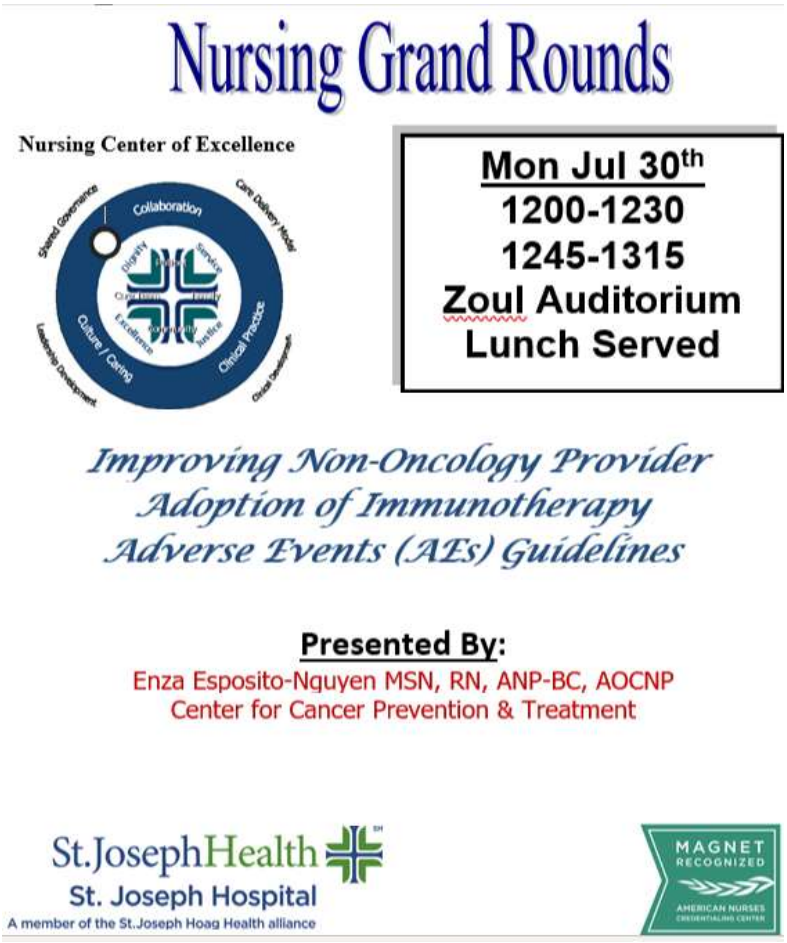
5



6

APPENDIX K

NURSING GRAN ROUNDS FLYER



APPENDIX L

STUDY FLYER

Are you a St Joseph Hospital Nurse or Physician interested in learning about immunotherapy treatment in cancer patients and how these patients can present themselves in your area of practice?
If the answer is yes, please attend any of the in-services throughout the hospital

Enza Esposito Nguyen, MSN, RN, ANP-BC Principal Investigator
Beth Winokur, RN, PhD Co-Investigator
714-734-6236

THIS PROJECT HAS BEEN DETERMINED TO BE EXEMPT FROM REVIEW AND APPROVAL BY THE CALIFORNIA STATE UNIVERSITY, LOS ANGELES INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

APPENDIX M
ONCOLOGY AGENT CLASSIFICATIONS CHART FOR ALL NURSES

Drug Classification	Action/Side Effects
Checkpoint Inhibitor (Immunotherapy) Nivolumab Pembrolizumab Ipililumab Avelumab Durvalumab Cemiplimab Atezolizumab	**Triggers the Immune System to Destroy Cancer Cells** ➢ Can cause "itis" ➢ Colitis/ pnuemonitis ➢ Hepatitis/endocinopaties
Chemotherapy Cisplatin Oxaliplatin Gemcytabine Capecitabine Fluorouracil Methothrexate Doxorubicin Etoposide Cyclophosphomide Docetaxel	**Destroys Cancer Cell During Cell Cycle** ➢ Can cause nausea/vomiting/diarrhea ➢ Numbness/ tingling of hands and feet ➢ Anemia/ neutropenia/thrombocytopenia
Targeted Therapy Erlotinib Afatinib Everolimus Rituximab Trastuzumab Ramucirumab Osimertinib Ceritinib Bevacizumab Crizotinib Alectinib Dabrafenib	**Inactivates Speficic Protein in Tumor Cells** ➢ Can Cause Rashes/nail changes ➢ Diarrhea ➢ Heart Failure ➢ Neutropenia ➢ Liver abnormalitites
Hormone Therapy Enzalutamide Anastrazole Abiraterone Lupron Tamoxifen Letrozole	**Blocks either estrogen/progesterone/testosterone** ➢ Causes hot flashes/ weight gain ➢ Osteoporosis ➢ Muscle aches
Growth Factors Filgratrim Epoetin Alfa Pegfilgastrim	**Stimulates Growth of Other Cells** ➢ Can Cause fever like symptoms ➢ Muscle ache

APPENDIX N

ONCOLOGY AGENT CLASSIFICATIONS CHART FOR EMERGENCY DEPARTMENT NURSES

PLEASE CIRCLE APPROPRIATE ONE

Drug Classification			
Checkpoint Inhibitor (Immunotherapy)			
Atezolizumab	Ipililumab		
Avelumab	Nivolumab		
Cemiplimab	Pembrolizumab		
Durvalumab	Other _____		
Chemotherapy			
Cisplatin	Doxorubicin	Methothrexate	
Capecitabine	Etoposide	Oxaliplatin	
Cyclophosphomide	Fluorouracil	Other _____	
Docetaxel	Gemcytabine		
Targeted Therapy			
Afatinib	Crizotinib	Osimertinib	Other _____
Alectinib	Dabrafenib	Ramucirumab	
Bevacizumab	Erlotinib	Rituximab	
Ceritinib	Everolimus	Trastuzumab	
Hormone Therapy			
Abiraterone	Letrozole	Other _____	
Anastrazole	Lupron		
Enzalutamide	Tamoxifen		
Growth Factors			
Epoetin Alfa	Other _____		
Filgratrim			
Pegfilgastrim			