Anne Burnett Marion School of Medicine at TCU

Immunotherapy-Related Toxicities and Renal Cell Carcinoma

Daniel Zeter, MS4

Mentor: Ina Patel, MD

Abstract

Research Question: What are the barriers to recognizing and diagnosing immunotherapy related toxicities and how does prompt initiation of steroids improve patient outcomes? In adult patients with advanced stage renal cell carcinoma, does timely recognition of immunotherapy toxicity including both PDL-1 and PDL inhibitors as well as CTLA-4 inhibitors (ex. ipilimumab, pembrolizumab, and nivolumab) and time to steroid treatment initiation lead to a better outcome? We will explore the barriers to both early toxicity recognition and beginning proper steroid treatment.

Background, Significance, and Rationale for the Question: According to National Comprehensive Cancer Network (NCCN guidelines), "Corticosteroids are the mainstay of treatment for most high-grade immunotherapy-related adverse events (irAE) and short-term use of corticosteroids to treat irAEs has not been shown to reduce anti- tumor efficacy." (NCCN version 2.2019) Immunotherapy is used to boost one's immune system response to target cancer cells. Prompt holding of these agents and initiation of steroids cause suppression of the immune therapy related toxicities to alleviate conditions. Our study focused on renal cell carcinoma, and the immunotherapies ipilimumab, pembrolizumab, and nivolumab to identify barriers in the onset of steroid treatment. Some barriers for starting steroids are fear of worsening hyperglycemia in diabetics, fear of counteracting immunotherapy response, delay of re-initiation of therapy once on steroids, a long taper over 4-6 weeks, etc.

Materials and Methods: Under the guidance of my mentor, Dr. Ina Patel, I will conduct a retrospective study analyzing adult patients (ages 18-75) being treated for renal cell carcinoma at UT Southwestern Medical Center and Moncrief Cancer Institute (MCI) from 2016-2021. This will be done using the Epic electronic medical record database from the clinic both in Dallas and Fort Worth locations. Patients will be identified for the study through a chart review, and their immunotherapy medication, possible toxicities, duration of steroid medication, timing of steroid medication after identifying toxicity, overall patient outcome, etc. will be documented. We will record this data, de-identify it and analyze this data with the help of a biostatistician from UT Southwestern Medical Center.

Results: Upon review of 201 patients with renal cell carcinoma (RCC) stage III/IV, the most common toxicity found was colitis (28.4%), followed by transaminitis (9.0%) and pneumonitis (9.0%). The most common methods for identification of toxicities was routine lab work performed before immunotherapy administration (30.4%), check-ins at regularly scheduled appointments (21.7%), and after-hour physician telephone lines (19.6%). Additionally, the average time from irAE identification to steroid administration was 1.45 days. Excluding toxicities found either at office appointments or on routine lab work, the average time to steroids from identification was 3.55 days.

Conclusion: Our study largely revealed that the current practices were successful in helping patients and providers identify irAEs in a timely fashion, leading to quicker steroid administration, and in turn, a sooner return to immunotherapy treatment. This study can be used as a blueprint and expanded to further investigate irAEs in other solid tumors as well as contribute to management of the ever-evolving immunotherapy landscape.

Research Question

What are the barriers to recognizing and diagnosing immunotherapy related toxicities and how does prompt initiation of steroids improve patient outcomes? In adult patients with advanced stage renal cell carcinoma, does timely recognition of immunotherapy toxicity including both PDL-1 and PDL inhibitors as well as CTLA-4 inhibitors (ex. ipilimumab, pembrolizumab, and nivolumab) and time to steroid treatment initiation lead to a better outcome? We will explore the barriers to both early toxicity recognition and beginning proper steroid treatment.

Hypothesis: We hypothesize that there are barriers to care that may hinder a patient's ability to seek prompt treatment for immunotherapy related toxicities. These barriers may include limited transportation, incomplete patient education, or cost of steroid treatments. We also believe that the duration between immunotherapy toxicity symptom onset and initiation of steroid treatment will be correlated with patient outcomes; the quicker that steroids are administered, the better for the patient.

Introduction, Significance, and Rationale

In 2021, there will be an estimated 76,080 people diagnosed with kidney cancer in the United States [1]. This cancer has seen a rise in incidence in the past 40 years and is now one of the top 10 cancers diagnosed each year. Amo[2]ng the kidney cancers diagnosed, over 90% patients will be affected by renal cell carcinoma (RCC) [3]. This specific form of kidney cancer is by far the most common and is difficult to treat. With improvements made in the past 30 years and the advent of newer individually targeted medications, the 5-year survival rate is still only around 74%, up from 57% in the 1970s [3].

The improvement in survival rate in RCC has been guided by advancements in treatment options. The former mainstay of treatment, interferon (IFN) and interleukin-2 (IL-2) have been replaced over the years by newer interventions with fewer side effects and improved therapeutic effects [4]. IFN and IL-2 only showed reproducible response rates in the range of 10-20%, which could be due in part to both the heterogeneity of RCC and the broad scale of these approaches [5,6]. Additionally, these medications were known to have many possible toxic effects, which limited their overall use, especially for IL-2 [7]. In 2005, the rise of a new drug, the multikinase inhibitor sorafenib, showed promise in the field of targeted immunotherapy. This drug was able to increase progression-free survival in patients with RCC, in situations where the former first line therapies had not been successful [8]. In addition to RCC, sorafenib showed success in combating advanced hepatocellular carcinoma and malignant melanoma [9,10]. Sorafenib started a wave development for new targeted immunotherapies, including ipilimumab, pembrolizumab, and nivolumab. These new monoclonal antibodies, also known as immune checkpoint inhibitors (ICI) work by binding various immune checkpoint proteins. Ipilimumab binds the CTLA-4 checkpoint protein and nivolumab and pembrolizumab both bind the checkpoint protein PD-1. Blocking of these checkpoint proteins allows for greater T-cell activation and proliferation, essentially taking the brakes off of the immune system and letting the body naturally fight against cancer cells[2,11]. In addition to ICIs offering a new approach to cancer treatment, these immunotherapy medications have shown great promise for the field of cancer treatment. Nivolumab began to be used in 2015 after it was shown to have longer

overall survival and fewer adverse events than the current preferred medications [12]. Also, nivolumab and ipilimumab have been used in combination to target a broader immune response and has been shown to provide a greater efficacy than previous first line medications in untreated advanced RCC [13].

An unfortunate side effect of upregulating the immune system with ICIs is the potential for immunotherapy-related adverse events (irAEs). Since these therapies can have systemic effects, there have been reported dermatologic, gastrointestinal, liver, pancreas, endocrine, lung, and neurologic toxicities associated with ICI use [14]. In a study done using the combined ipilimumab and nivolumab, 91% patients reported an irAE, with 36% of patients requiring hospitalization due to their irAE [15]. In this case, some of the toxicities included diarrhea, endocrinopathies, hyperglycemia, myasthenia gravis, and autoimmune meningitis.

When using ICIs, it is inevitable to expect toxicities to arise at some point. In the event of an irAE, the National Comprehensive Cancer Network guidelines recommend using corticosteroids as treatment, essentially to dampen the immune system after it has been ramped up by ICI medication. The use of short-term corticosteroids has not been indicated in worsening the prognosis for the anti-tumor effects of ICI medications (NCCN version 2.2019). There are increasing amounts of studies showing the resultant irAEs from ICI treatment [16,17], so there needs to be a focus on how to predict and mitigate these irAEs before they become detrimental and irreversible for patients.

There have been recommendations made for specific toxicities based on a grading scale I-IV that shows the preferred corticosteroid treatment, whether or not to continue the ICI with corticosteroid use, and when hospitalization or referral is necessary [18]. However, with the growing range of ICI medications being developed and individualized treatment plans for patients, the authors of these recommendations noted that additional clinical data will be needed to develop definitive answers to treating irAEs. There are still multiple scenarios where the appropriate dosage and timetable is not yet known, increasing the need for more research in this field [19]. Some researchers have approached this problem by using predictive modeling to identify patients receiving treatment that are at a higher risk for irAEs. These models include

looking at a patient's body composition or full blood count to predict toxicity potential [20-23]. There is still a need, however, for widespread analysis and testing before predictive models could be implemented as an option for physicians.

The main barrier in treating irAEs identification of toxicites in a timely fashion, as prompt holding of these ICI agents and initiation of steroids alleviates many of the associated toxicities [24]. Even with predictive models and accurate dosage algorithms, there will always be some barriers in the way (fear of worsening hyperglycemia in diabetics, fear of counteracting immunotherapy response, delay of re-initiation of therapy once on steroids, etc.). Identification of these barriers is crucial to starting patients on corticosteroid treatment as soon as possible whenever irAEs arise, in order to return the patients to their immunotherapies to continue treatment. While there has been a large volume of research done on toxicities associated with ipilimumab, pembrolizumab, and nivolumab, in association with malignant melanoma, there has been less done in the field of renal cell carcinoma [11,15,21,23,24]. For a cancer that affects such a large number of patients each year, there are thousands of individuals that will be treated with ICIs and experience irAEs. Identifying specific barriers to noticing toxicity onset and initiating the prompt start to corticosteroid treatment is critical in helping these patients receive the full effect of their ICI regiment.

Materials and Methods

Subject Identification

Potential individuals for this study were identified using the Epic electronic medical record database from UT Southwestern (UTSW) Medical Center and Moncrief Cancer Institute (MCI). The following criteria were met by all of those selected for the study: (1) a patient under the direct care of a physician at MCI between the years 2016-2021, (2) between the ages of 18-75 at diagnosis, (3) received a diagnosis of advanced stage renal cell carcinoma, and (4) was prescribed one of the medications of interest (ipilimumab, pembrolizumab, and nivolumab). Using the Epic database, UTSW records were able to pull a list of patients that met these specific criteria. This list included a total number of 233 patients. From this list, we were able to identify specific patients (via Medical Reference Number, and date of birth) and immediately see their diagnosis as well as immunotherapy type, dosage, and time. This initial step was the basis for our data collection. Our initial goal was to recruit over 95 patients for this study from both the MCI database and the UTSW database. This was the goal enrollment for a correlational study of medium effect size, with α=0.05 [25]. We were able to meet this goal and proceeded with data collection.

Data Collection

After eligible patients were identified for the study from the UTSW database, we had a total of 233 patients, surpassing our initial goal of 95 patients. For each patient, a meticulous chart review was completed. For each patient, the following data points were noted: exact diagnosis (i.e. grade 3, grade 4), immunotherapy type, immunotherapy dosage, immunotherapy duration, immunotherapy adherence, type of immunotherapy reaction (if applicable), duration in time from immunotherapy onset to reaction onset, duration in time from onset of reaction to medical intervention, medical visits/ medical guidance for toxicity-related care, prescribed steroid regimen for toxicity (type, dose, duration), hospitalization(s)-related to immunotherapy-toxicity, outcome from irAE, changes made to immunotherapy medication (i.e. if medication was halted due to toxicity, when did it resume and if changes to dosage/schedule were changed), overall patient outcome, comorbidities, and noted barriers to medical services (i.e.

patient has limited access to medical services and could not receive prompt guidance for irAE). This data was collected in a de-identified excel sheet. We organized the data collection in rows to reflect each unique patient and used columns for individual data points. Much of the information collected came from oncology office visit notes at UTSW. These were a clear roadmap for the patient's care and allowed us to see gaps in treatment that potentially reflected irAEs. If information was not readily available from oncology visit charts, a chart review was perfomed looking for hospital admissions or emergency room visits pertaining to irAEs. Additionally, utilizing the medication history tab, it would be evident if the patient had been put on a steroid regimen in the past to possibly identify irAEs. Occasionally, patients would be seen at hospitals outside the UTSW system and Care Everywhere could be used to provide details of these visits. For many patients in this study, the information required was readily available and easy to assess.

Software Concerns and Patient Confidentiality

All the research was performed on a UTSW encrypted laptop that had password-access to the medical records. Identifiable patient information was de-identified after initial identification of eligible participants in the study. This data was then kept unidentified for the remainder of the study. All trainings for UTSW software security and patient information safety were completed prior to beginning data collection. Additional trainings were completed throughout the duration of the study to maintain compliance with UTSW security management.

Statistical Analysis

Statistical analysis was performed in Excel. For the first portion of this study our main goal was to characterize barriers to identification of irAEs, identify possible comorbidities, and calculate the time from identification to steroid onset. We are currently working to expand our analysis with help from UTSW biostatisticians to look at correlational outcomes between identification time and disease progression/prognosis. We believe that we will see better results overall for patients who begin treatment at an earlier stage, and who are able to identify irAEs quickly and begin steroid interventions promptly.

Results

Patient Demographics

The total number of patients in our study totaled 232. The patients were included from a data pull performed by statisticians at UTSW based on our inclusion criteria stated in the above Methods section. After careful review of each patient and their electronic medical record, 200 patients were including in our final study. For the 32 patients that were excluded, many met exclusion criteria including: age, date of diagnosis, stage of diagnosis, or immunotherapy type.

Of the 200 patients, their mean age was 62.2 years old at the time of diagnosis, 61 (30.5%) were female, and 139 (69.5%) were male. 167 of the patients were white (83.5%), with 20 being Hispanic white (10%), 9 patients were African American (4.5%), 5 patients were Asian (2.5%), and 18 were classified as other (9%). These patients were all diagnosed with stage III or IV renal cell carcinoma, 56 (23%) with stage III and 144 (72%) with stage IV.

Comorbidities

The four most common comorbidities were hypertension (126 patients; 63%), hyperlipidemia (67 patients; 33.5%), type 2 diabetes (55 patients; 27.5%), and gastroesophageal reflux disease (27 patients; 13.5%).

irAE Types

When looking at the types of irAEs there were a broad range, including encephalitis, hypophysitis, nephritis, hepatitis, dermatitis, mucositis, colitis, gastroenteritis, polyarthritis, adrenal insufficiency, pneumonitis, bilateral knee effusions, and pancreatitis (*Figure 1)*. In total, 66 patients, or 33% of the patients included in the study experienced immunotherapy related adverse events, occasionally experiencing more than one. The two most common were colitis (19 patients; 29%) and hepatitis (11 patients; 16%). Among the patients with irAEs, only 17 experienced hospital admission due to their adverse events, meaning 8.5% of all patients had an irAE that required admission, and 24% of patients with irAE required hospital stays.

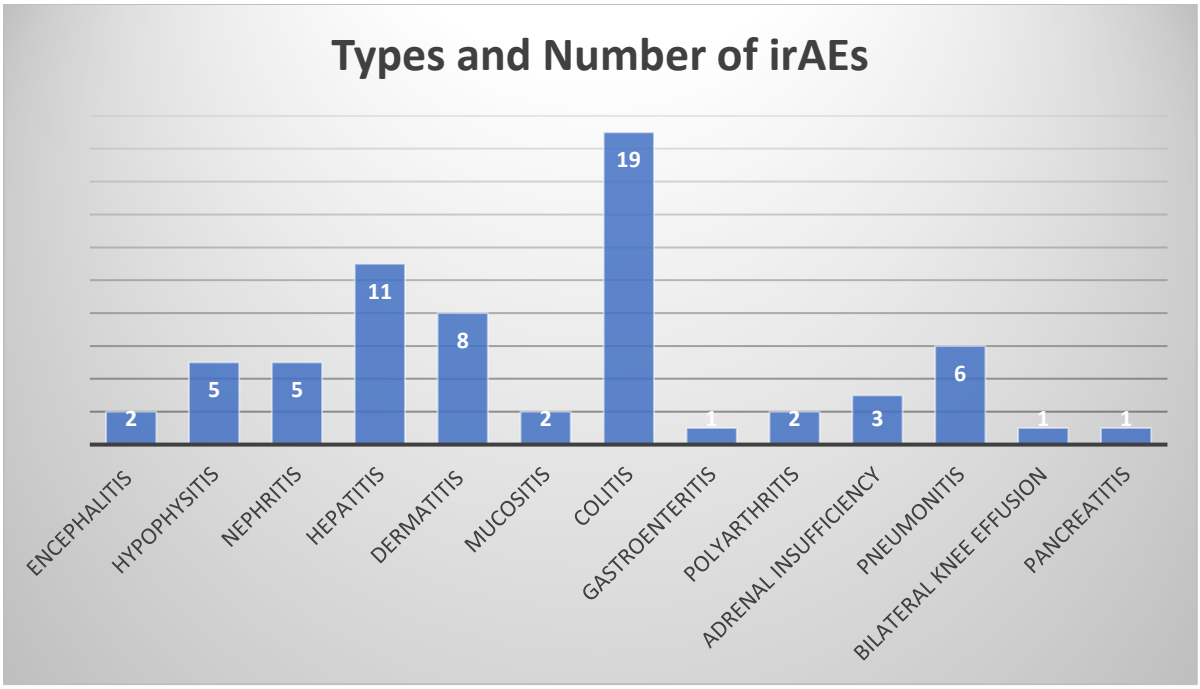

Figure 1: Type and Number of irAEs.

irAE Identification

The next portion was to look at barriers to irAE identification, and the mode of identification. The 4 main categories patients could be grouped into were routine lab work, office visit, emergency room visit, and telephone communication. Routine lab work were patients that had asymptomatic irAEs found on lab work before receiving their immunotherapy. Office visit patients were found to have irAEs during regularly scheduled office visits when asked for any changes or as part of their review of systems. Emergency room visits included patients who noted irAEs and presented to their local or UTSW emergency room for treatment. Telephone communication included patients who noted irAEs or changes to their current symptoms and notified their oncologist via after hours physician lines. 14 patients (30%) of patients had irAEs found via routine lab work, 10 (22%) via office visit, 11 (24%) via emergency room visit, 9 (20%) via telephone communication, and 2 (4.3%) included multiple approaches (*Figure 2)*.

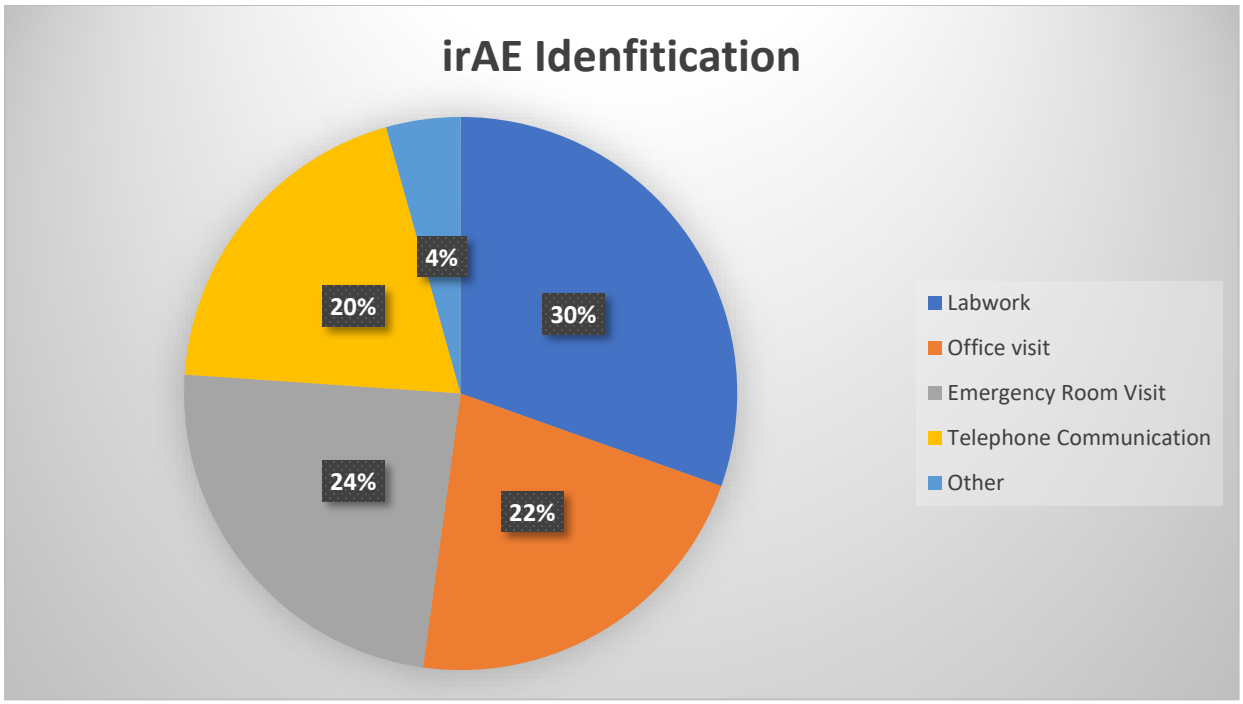

Figure 2: irAE identification. Types listed on right side of figure, represented as percentages in pie chart.

Onset of Steroid Treatment Time

The last key data point was to identify the time of symptom onset/identification to steroid regimen. We looked across the board at patients with irAEs and how soon they received steroids, and the average time was 1.4 days. We then excluded patients that were identified through routine lab work or office visits, and found they had an average time of 3.5 days from symptoms onset to steroid administration.

Discussion

Data Interpretation

From our results, it was clear that the hypotheses set forth from the initiation of the project were in fact true. The average age of our patients, with a male predominance was like what is seen nationally, representing a good sample size. Our total number of patients was also sufficient to draw conclusions from.

Identifying the most common irAEs was very important, especially as phase two of the study will take shape. Many of the irAEs listed to not have a readily identifiable symptom (hepatitis, colitis, encephalitis) for patients to identify. Many of the irAEs listed could simply be subtle changes from a patient's baseline that were a result of the immunotherapy. If all the irAEs were dermatitis, for example, it would likely be easier to find a solution to barriers in steroid treatment and education to the patient. Additionally, there was a very broad overview represented amongst the irAEs. This was to be expected as patients often have various reactions to immunotherapy agents. Among all patients included in the study for being treated with immunotherapies, a small percentage (8.5%) required hospital admission for their irAE. We imagine this was largely due to prompt management by providers to recognize irAEs either at the office or via lab work and help treat patients before their symptoms became too severe.

The identification of irAEs showed that a lot of the work that is currently being done at UTSW oncology clinics is working. Over 50% of the irAEs identified were directly due to systems in place to catch adverse reactions to medications—lab work and routine visits. The lab work was crucial in identifying the large proportion of patients that experienced hepatitis or nephritis. Many of these patients were asymptomatic and without lab work the irAE would not have ben identified. Additionally, many patients that presented to their regularly scheduled visits were able to express concern over new symptoms or were asked a series of questions throughout their visit that elicited signs of adverse reactions. Another 20% of patients utilized telephone communication, often weeks out from their next regularly scheduled visit with their oncologist. This patient education step is key to inform patients of their communication options. That leaves a remaining 25% of patients that presented to their local emergency room

for evaluation of new symptoms. For many of these patients it was due to an acute change in symptoms or abrupt onset in symptoms. Patients were not in this category if they received a workup at an oncology office before being sent to an emergency room for further evaluation.

Lastly, the time to steroid administration further showed the efficiency of communication between patient and provider and the importance of routine lab work for these patients. When looking at the data across the board the mean time of administration of steroids after identification was 1.4 days. The low number largely reflects the many patients seen in clinic that were started on steroids later that same day after an irAE was identified. When controlling for these situations, the average time of administration was 3.5 days. This reflects the delay in treatment when patients may have been met with new symptoms but did not connect significance with their treatment due to lack of patient education on the part of the clinic or it could reflect an initial presentation that was not severe enough to warrant medical attention. This is still a low timeframe for identification to steroid treatment and was lower than expected at the beginning of this study.

The data analysis is not complete currently, however. There is current work being done on relationships between specific immunotherapy type, outcome of patients, and severity of irAEs.

Originality

The idea behind this project in the setting of renal cell carcinoma was novel at its origination. There had been other projects looking into immunotherapies, immunotherapy efficacy, and immunotherapy adverse events, but never looking specifically at barriers patients may face in identifying irAEs. Our hope was to use this project as a blueprint for other areas of oncology treatment, i.e. exploring various immunotherapies for other solid organ tumors that frequently have irAEs. Additionally, the second portion of this project which remains an area of future research that will look at specific interventions that can be made in the delivery of care at oncology clinics within the UTSW system will be novel in looking at the effectiveness of various mechanisms to decrease time to steroid administration. Like phase one, the model could then be translated to other areas within oncology care.

Impact

The initial impact of this project simply was further reaffirming the current practices in oncology clinics at UTSW. The short time frame between identification and administration of steroids reflects efficient current practices. The second phase of this study will hopefully dive deeper into how specifically to reduce this time frame even more and identify ways to help the outlier patients.

Strengths

This study did a great job at identifying common irAEs for patients being treated for renal cell carcinoma. This study was also able to accurately look at the ways irAEs are identified in the clinic and outside the clinic, and how this effected the time it took from identification to administration of steroids for patients.

Weaknesses

With any retrospective study there were limitations. The largest limitation is that this study reflects a very specific subset of patients. They were all treated here in Dallas/Fort Worth at a UTSW center. With that being said, the study design could be adapted for other hospital systems or clinics, but the results from this study are not representative and cannot be generalized to other systems. Another limitation is the retrospective nature of this study. While through data collection from the electronic medical record we were able to identify a lot of the key points in a patient's medical history, there was extrapolation that took place. If the data was being collected in a prospective fashion it would be easier to gain understanding to how patients were viewing the patient education and how they were able to identify irAEs in real time.

Future Directions

This study originally had two goals. The first being to identify barriers to steroid treatment for irAEs in patients being treated for advanced stage renal cell carcinoma. The second being to test an intervention in patient education to help patients identify irAEs and seek treatment. While there was not a formal application of the second goal in this study, that is largely the next step for this study.

Our hope is that the research conducted in this study can be used as a blueprint for other avenues within the oncology space. Immunotherapies are a rising treatment option for many solid organ tumors, and immunotherapy adverse events are a common risk for these options. Identifying what these patients are most likely to experience and identifying how to help patients receive appropriate and timely care is crucial to their overall treatment. While this study was good at looking specifically at renal cell carcinoma being treated at UTSW facilities there is little generalization to other oncologic treatment centers around the country.

This study will hopefully be continued by another student at Burnett School of Medicine to further test out ways of improving patient education around irAEs. It was clear from this study that the systems put in place, i.e. lab work and office visits, did a good job at identifying over half of all irAEs in the last five years. It is the remaining 40-45% of patients that further education could help identify irAEs and decrease the time it takes for them to receive appropriate steroid treatment. Those two areas are the largest in terms of future directions for our study.

Conclusions

Major Findings

The main finding in this study showed that the current work being done at UTSW oncology clinics is largely successful in the identification and treatment of irAEs. With current practices of routine clinic visits and routine lab work, over 50% of the irAEs were found immediately and treated appropriately. When looking at the other nearly 45%, patients utilized telephone communication and emergency room visits for most of their care to be treated for irAEs. Further work in patient education and awareness of possible symptoms that could be early signs of irAEs will continue to be an area of improvement, alongside the continuation of routine office visits and lab work.

Implications

The implications of this work will not immediately change the delivery of care to individuals at UTSW. It will, however, serve as the basis for a second stage in this study that can look at measurable outcomes in patient education pertaining to irAEs. The results showed that a lot of the current work is sufficient in catching early irAEs or asymptomatic irAEs, and the area that can be improved is in patient self-identification of adverse reactions.

Compliance

This study received IRB approval through MCI/UT Southwestern and TCU Burnett School of Medicine. All trainings were kept up to date throughout the entirety of this study.

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