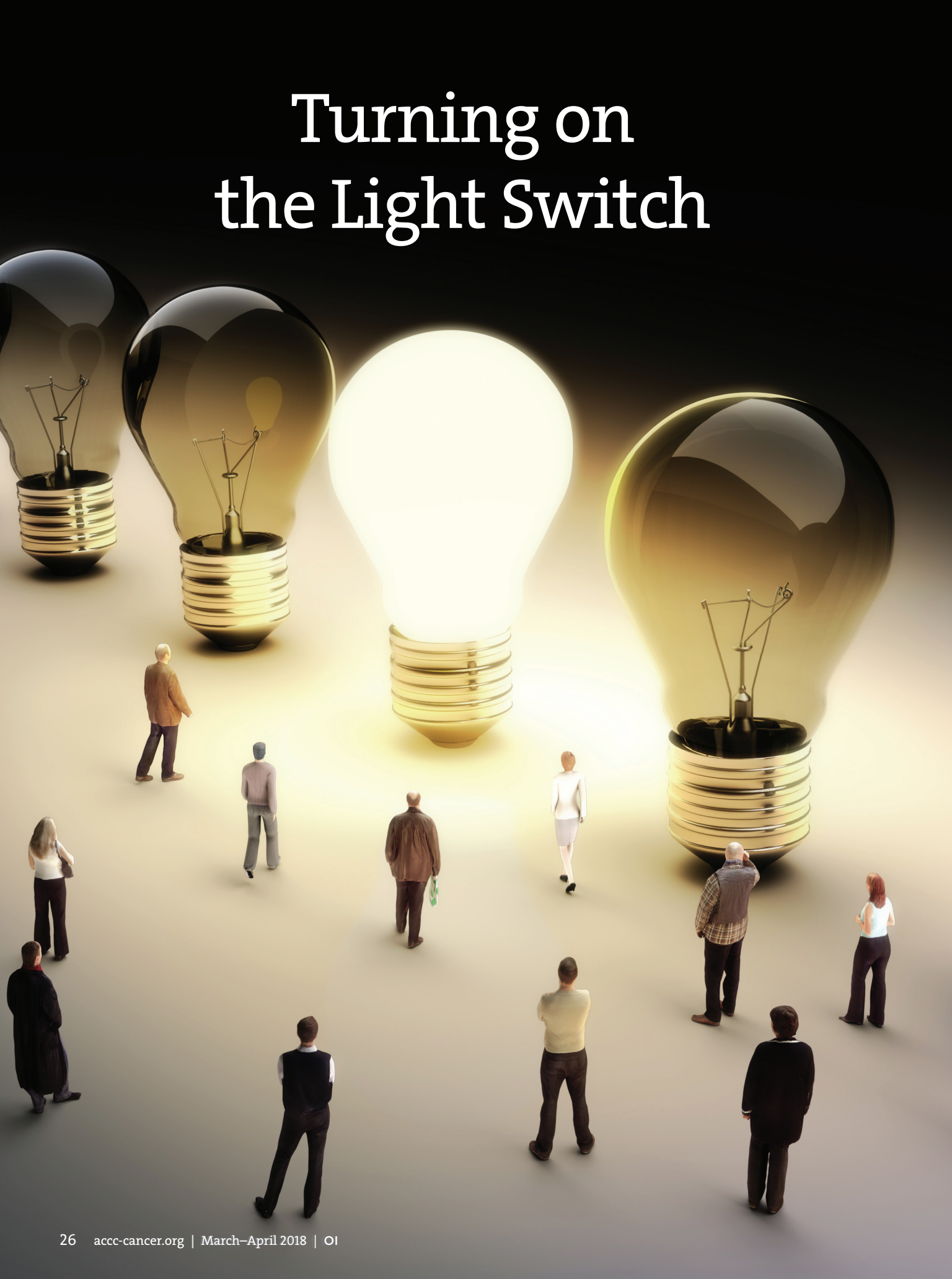
Turning on the Light Switch



BY ANN MCGREAL, RN

A model immunotherapy program at an oncology practice

During the past 3 years, medical journals have virtually exploded with headlines about immunotherapy and cancer, and it all started on March 25, 2011, when the U.S. Food and Drug Administration approved ipilimumab injection (Yervoy®) for the treatment of unresectable or metastatic melanoma. Though the breakthrough was huge news in the melanoma space, it had few immediate repercussions for the rest of oncology. That changed in 2015 with the approval of the PD-L1 checkpoint inhibitor nivolumab (Opdivo) for the treatment of patients with advanced non-small cell lung cancer. Most early studies found that checkpoint inhibitors showed all of the potential of earlier immunotherapeutic agents with far less toxicity. However, though immunotherapy is the biggest breakthrough in oncology in recent decades, this new treatment modality brings new toxicities for cancer patients.

Just as mainstream media was quick to herald the successes immunotherapy offered in the fight against cancer, so, too, was the media quick to report on its adverse effects. For example, a 2016 *New York Times* article shared the story of Chuck Peal, a patient on combination immunotherapy who found himself gravely ill in an emergency room and being treated by physicians

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unfamiliar with this class of medications.[1] Peal's cancer was gone, but the toxicities left him seriously ill and physicians baffled about what to do for him. The article quoted John Timmerman, MD, an oncologist and immunotherapy researcher at the University of California who had recently lost a patient to side effects of her immunotherapy treatment. He described his patient's response as "a mass riot, an uprising" of her immune system and went on to say, "We've heard about immunotherapy as God's gift, the chosen elixir, the cure for cancer. We haven't heard much about the collateral damage."[1]

As these new therapies were more widely adopted, issues arose at emergency rooms (ERs) where immunotherapy patients were sometimes forced to go for treatment of toxicities. Even when immunotherapy patients informed ER staff that they were being treated with immunotherapy for cancer, ER staff often made the assumption that these patients were being treated with chemotherapy. Accordingly, pneumonitis was treated with antibiotics; diarrhea was treated with conventional methods. Situations like this were so alarming that pharmaceutical companies developed "wallet cards" as part of risk evaluation and mitigation strategy (REMS) programs so that immunotherapy patients had something to show healthcare professionals if they had an emergent medical problem.

Having accrued a high number of patients to the ipilimumab trials, Advocate Medical Group (Formerly Oncology Specialists S.C.), Park Ridge, Ill., had experienced its share of immune-mediated toxicities. In the beginning, these were isolated to melanoma patients, and research protocols were in place to assist with the challenges of managing the toxicities. But by 2015, with our practice facing an unprecedented expansion of immunotherapeutic agents and indications and with the understanding that many of our physicians had never prescribed an immunotherapeutic agent (Figure 1, page 29), we realized that development and implementation of an immunotherapy program was not only a good idea but an immediate need to ensure safe, evidence-based treatment for our patient population. As our immunotherapy program was being developed and in its infancy, professional organizations like Association of Community Cancer Centers,[2–6] the Oncology Nursing Society,[7,8] the National Comprehensive Cancer Network, and the American Medical Association also recognized the urgent need to educate and prepare clinicians to be ready to treat these immunotherapy patients.

Educating Our Staff

The first challenge we faced in the development and implementation of our immunotherapy program was how to most effectively and efficiently educate our medical staff. We addressed this through a peer-to-peer process. Physicians who were early prescribers of immunotherapeutic agents educated their peers and also reached out to the medical community as a whole. Understanding that support would be needed in many other medical specialties, including but not limited to endocrinology, gastroenterology, cardiology, pulmonary, dermatology, and emergency medicine, we also used this peer-to-peer process to educate our nurses. At the rate that immunotherapeutic agents are being approved and introduced to the market, it is challenging to keep the entire staff—from physicians to the billing department—aware of all indications and the requirements for each indication. To help, our pharmacy department developed an immunotherapy flowchart (Figure 2, page 29). Our pharmacy staff frequently updates this tool, which is located on a shared computer drive for easy access.

Our oncology practice is modeled on a primary nurse system, so the same nurse treats the patient from start to completion of therapy. Policies and procedures support this model, with our treatment plans acting as the backbone to our treatments. These treatment plans give nurses orders for labs scans, dose reductions, supportive medications, and sequencing of medications. A new treatment plan was created for each immunotherapy regimen.

Accordingly, development of our immunotherapy program started at our practice's foundation: its policies and procedures. As in most oncology practices, our education focused on chemotherapy and biotherapy. Even our basic education information, such as reasons for patients to call the clinic, discharge instructions, and follow-up standards, were outdated and incomplete because they did not include immunotherapy. Every policy and procedure had to be updated to include immunotherapy. Most important, all staff and patient education resources had to be revised as well.

Developing a Robust Portfolio of Tools

As staff got to work updating existing information, we realized that though pharmaceutical companies had developed and published very good patient education materials on their specific medications and potential side effects, education on immunotherapy in general was sparse and not designed for the lay consumer. Thus, we first developed an introductory tool for patients that defined and explained immunotherapy (Figure 3, page 30). To help patients understand the importance of reporting adverse symptoms and side effects early, staff used the metaphor of a light switch. Immunotherapy turns on the light (i.e., the immune system) to fight cancer, which is good. However, sometimes our bodies cannot turn the light off when it starts overworking. If a light is left on, it burns out and so will organs affected by the immunotherapy. Adapting education material from Bristol Myers Squibb, the back of this tool features a diagram of the human body with corresponding side effects (toxicities) related to each organ. Nursing staff use this diagram and patient wallet cards to discuss specific toxicities and how to recognize them.

Next, we developed a tool to educate patients on when they should call the clinic. Specifically, our immunotherapy patients are instructed to call their nurse or physician if they experience any of the following:

- **Fever greater than 100.4°F with or without chills** not relieved when you take ibuprofen 400–600 mg or Tylenol 650 mg.
- **New onset cough or chest pressure.**
- **Shortness of breath** that is more than your usual way of breathing.
- **Diarrhea**; that is, more than three diarrhea stools per day that does not resolve with one dose (2 tablets) of Imodium-AD, or any blood or mucus in your stool.
- **Nausea or vomiting** that results in your inability to take in

food and fluids for more than 24 hours.
- **Changes in your vision** or increased sensitivity to light.
- **Skin rash** or intense itching without rash.
- **Extreme fatigue** that limits your normal activity.
- **Headache** not improved by normal remedy.
- **Muscle or bone/joint aches and pains** that are not relieved with pain medication.
- **Weakness in legs (feet) or arms (hands)**—difficulty doing your normal daily activities

Patients are given a clinic number to call 24 hours a day and told that if they call after regular hours and have not heard from a doctor within one hour to call again. Patients are also told that if they have symptoms that are worse than those mentioned above, they are to go immediately to the local ER and present a wallet card to let staff know that they are being treated with an immunotherapy agent.

At this point, staff realized that it would be necessary to document in the patient's electronic health record (EHR) when patients received this education and instructions. Based on existing resources developed by various pharmaceutical manufacturers, we developed a patient immunotherapy checklist to use when patients are discharged from the infusion center (Figure 4, page 31). Patients fill out this checklist after their first infusion and then prior to each infusion thereafter. Staff enter the information into the EHR, and providers can then compare patient responses from one treatment to the next. This checklist triggers the conversation about toxicities and allows our staff to easily identify and address any changes.

Figure 3, page 30, is another education tool we developed for patients after they complete their first infusion. This tool lists the

Figure 1. Physicians at Advocate Lutheran General Hospital Prescribing Immunotherapy by Year

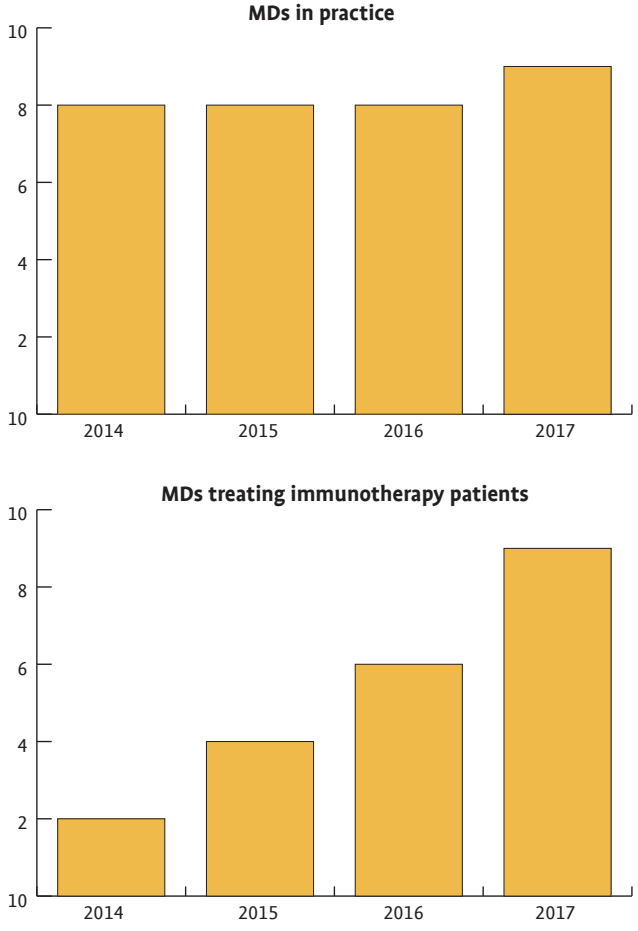

Figure 2. Immunotherapy Flowchart of FDA-Approved Indications

	Melanoma		NSCLC	HNSCC	Renal Cell Carcinoma	Classical Hodgkins	Urothelial Carcinoma	MSI-H
pembrolizumab	Unresectablet/ metastatic c	200mg q3w	200mg q3w**	200mg q3w		200mg q3w	200mg q3w	200mg q3w
nivolumab		240mg q2w	240mg q2w	3mg/kg q2w	240mg q2w	3mg/kg q2w	240mg q2w	240mg q2w
nivolumab + ipilimumab		nivo1mg/kg + ipi 3mg/kg						
ipilimumab	Adjuvant	10mg/kg q3w x4, then q12w						
atezolizumab			1200mg q3w				1200mg q3w	

** Tests + for PD-L1
1st line NSCLC whose tumors have high PD-L1 expression (TPS ≥ 50%)
2nd line NSCLC whose tumor have high PD-L1 expression (TPS ≥ 1%)

most common toxicities and practical ways for patients to respond to them before calling the clinic. This tool is located on our shared drive and is personalized for each patient and copied and pasted into their EHR at discharge.

Figure 6, page 33, is a form that our staff uses to document patients on dual immunotherapy (ipilimumab and nivolumab) for which the incidence of grade 3 and 4 immune-mediated toxicities is much greater. To address this increased chance of adverse toxicities, our treatment plan requires a weekly check on the patient for the first 15 weeks of treatment. Using this form, nurses perform a system-by-system weekly check either by phone or in clinic, at the discretion of the nurse.

As we developed and implemented our immunotherapy program, staff recognized that the treatment of immune-mediated toxicities with high-dose prednisone was not addressed in our treatment plan. Moreover, this information was difficult to document in the EHR so that all members of the care team are aware of what toxicity we are treating, the steroid dose, and taper schedule. To address these issues, our staff developed a steroid taper treatment care plan. In brief, here's how this tool works.

Using this online tool, staff first identify the toxicity. Next, staff document the starting dose on prednisone. The treatment plan is in the EHR, so all physicians and nurses covering this patient are aware of the symptom dose and taper schedule. Patients are required to call the nurse with each dose decrease, and the nurse charts this interaction in the EHR so that the information is captured. All patients are prescribed prednisone 10 mg (so, for example, if the dose is 60 mg, patients take six tablets). For each prednisone dose entered, there is a corresponding notes section for staff to fill in with the appropriate information. For example, one note might read: LFT results at grade 1, so dose reduced to 40 mg daily.

Evaluating and Improving Our Immunotherapy Program

Our practice officially started its immunotherapy program in September 2016, and we evaluate the program and its tools on an ongoing basis. The importance of our immunotherapy program

Figure 3. Patient Education Sheet

Advocate Medical Group Oncology Specialties

What is Immunotherapy?

Immunotherapy uses your body's own immune system to fight cancer cells. This treatment is designed to produce immunity to a disease or enhance the resistance of the immune system to an active disease process, such as cancer. These medications include a family of drugs called checkpoint inhibitors. Your body has natural "checkpoints" in place to hold the immune system in check so it does not overwork.

These medications work by activating your T lymphocytes, the white blood cells that go after foreign invaders, to target the tumor cells.

This is like turning on the light switch.

It is important to know that once activated the light switch will remain on. This is necessary to have the greatest effect against your cancer. However, this may result in reaction against your normal healthy tissues.

So imagine if you turn on a light in your home and you cannot turn it off:

- Activating the immune system: immune therapy medications turn the switch on
- However, it also stops your body's natural ability to turn the switch off.
- Eventually, without some intervention, the light will burn out (can cause damage to your normal healthy tissue).

This is a very simple explanation of how immune therapy works in your body. It is very important that you communicate with your nurse and physician when any side effects occur.

Possible Side Effects

You may experience very serious side effects related to the immune activation. We want you to become familiar with what to look for to catch these reactions early.

Our goal is to **keep the light switch on** to have the greatest effect against your disease. However, normal healthy tissues can also react to this immune system activity.

Healthy tissues most often affected by the immune response are: the GI tract, especially the colon, liver, lungs, and nervous (neurologic) and hormonal (endocrine) systems.

Other general side effects include eye problems, fatigue, muscle/joint aching, and fever.

Mild side effects are expected. It is very important to report any moderate to severe symptoms to your doctor or nurse as soon as possible since they can get worse very quickly. Do not wait to call if symptoms get worse.

Figure 4. Patient Immunotherapy Checklist

NURSING IMMUNE-MEDIATED ADVERSE REACTION CHECKLIST

Patient Name: _____ **Date:**_____

Please complete prior to every dose.

Gastrointestinal (Digestive)	Response		Notes
	Yes	No	
Has your appetite changed?			
Do you have nausea or vomiting?			
How many bowel movements are you having a day?	**Number:**		
Is this different from normal?			
Are your stools loose or watery or foul-smelling?			
Do you have pain or cramping in your abdomen?			
Have you seen blood or mucus in your stools?			

Skin	Response		Notes
	Yes	No	
Does your skin itch?			
If yes, does it keep you up at night?			
Do you have a rash? If yes, where?			

Respiratory	Response		Notes
	Yes	No	
Do you have difficulty breathing or shortness of breath?			
Are you coughing?			
Do you have chest pain?			

Neurologic	Response		Notes
	Yes	No	
Are you having difficulty getting up from a chair?			
Do you have weakness in your hands, legs, or muscles?			
Are you having trouble with gripping, dropping, or picking things up?			
Are you having difficulty walking or are you unsteady?			
Are you having numbness or tingling in your hands or feet?			
Are you having problems with your memory or confusion?			
Are you having seizures or stiff neck?			

General	Response		Notes
	Yes	No	
Have you started taking new medications? (prescriptions, herbal, over the counter)			
Are you able to perform your normal activities?			
Are you having difficulty sleeping?			
Do you have headaches that do not go away?			
Have you felt dizzy or lightheaded?			
Are you bleeding or bruising more than usual?			
Are you having any flu-like symptoms? Fever?			
Do you have aching or weakness in your muscles or joints?			
Have you noticed problems with your eyes or vision?			
Have you noticed an increase in fatigue?			
Are you having changes in your libido (sex drive)?			

Figure 5. Patient Home Discharge Instructions

Advocate Medical Group
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7900 N Milwaukee Ave at 16 Niles, Il 60714
847.268.8200

PATIENT HOME DISCHARGE INSTRUCTIONS

Patient's Name: _____ Physician: _____
Therapy Date: _____ Nurse: _____

Immunotherapy Medications administered:

Reasons to Call:
1. Diarrhea
   - More than 3 diarrhea stools in one day
   - Any blood in your stool
2. Rash or itchiness
   - Raised red rash with itching or itching with no rash
3. Shortness of breath, new cough, or chest pain
4. Flu-like symptoms that do not resolve
   - Headache, fever, chills, joint pain
5. Any problems, questions, or concerns

Symptom Management Medications:
1. Imodium – 2 tabs after 1st diarrhea stool, 1 after each subsequent stool
   - MUST CALL IF YOU NEED MORE THAN 2 DOSES
2. Ibuprofen – 3 tabs (600 mg); or acetaminophen 2 tabs (650 mg) every 6-8 hours as needed for headache, joint pain, chills, fever
3. Prochlorperazine (Compazine) 10 mg – take one every 6 hours as needed for nausea
4. Diphenhydramine (Benadryl) 25 mg – take 1-2 tablets every 6 hours for itching

Things to Remember
1. Drink plenty of fluids
2. Good hand washing
3. Sunscreen SPF 30 or higher

Call our 24-hour number with any problems, Monday-Friday 9 am-5 pm, and ask for your nurse.
After hours or weekends, ask for Dr. _____ or the doctor on call. 847.268.8200

cannot be overstated. In two short years, our practice went from two physicians ordering immunotherapy to 10 physicians ordering these cutting-edge treatments for their patients. Consistent use of the patient education tools we developed is key to our success and to ensuring that our patients have a good understanding of immunotherapy, its possible side effects and toxicities, and when to contact the clinic.

As part of our evaluation process, we gave 35 patients a set of scenarios and then asked them to check the box those that required them to call the clinic. Patients were correct 85 percent of the time.

We also asked our physicians, nurses, and patients to comment on the new immunotherapy program and the patient education tools developed. Feedback was positive. For example, physicians shared that implementation of the steroid taper treatment care plan resulted in safer treatment care that is more seamless. Nurses agreed that the immunotherapy program helped with patient education and documentation, although they requested a few modifications; for example, "Fatigue" was added to the patient questionnaire checklist. Based on nurse feedback, we also developed a way to compare the patient questionnaire checklist from one treatment to the next, leveraging our EHR. Patients found the resources helpful and shared that these tools made it easy to review toxicities with medical staff.

The immunotherapy program has been in place for one year, and our practice is heading into its third round of evaluation.

Figure 6. Supportive Care Treatment Plan: High-Dose Steroids for Immunotherapy Toxicities

SUPPORTIVE CARE TREATMENT PLAN
High-Dose Steroids for Immunotherapy Toxicities

Name: _____ **DOB:** _____

Diagnosis: _____

Allergies: _____

Weight: 63.2 kg

Reason of treatment:
- Skin toxicities d/t immune-mediated rash
- Immune-related pneumonitis
- Diarrhea d/t immune colitis
- Elevated LFT d/t immune hepatitis
- Endocrinopathy (body joint aches, fever, headache)

Drugs:

Prednisone (0.5mg – 1mg/kg)	po	10mg	take _____ tablets daily

Taper Directions: Reduce dose by 1 tablet

- q 3 days begin when rash and itching have resolved
- q 3 days if improved 02 sat, relief of SOB and/or cough
- q 3 days if no diarrhea or abdominal cramping
- weekly if LFT remain normal
- q 3 days begin when symptoms resolve

Requested Labs:	Tests	When
	Comp Panel	weekly (for hepatitis only)
	Quantiferon™ TB Golf (QUANTF)	once for GI only

Other: If high-dose prednisone is ordered, for GI toxicity, precert for infliximab

Required communication with MD or Primary Nurse: prior to each decrease in dose

Electronically signed by:

Date Signed:

The biggest takeaway from this program has been the importance for the medical community to stay up to date with medical science. We need to be open to change and well-read in order to give the best possible evidence-based care to our patients.

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