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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

From a Patient Advocate's Perspective: Does Cancer Immunotherapy Represent a Paradigm Shift?

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Abstract

Purpose of Review In 2016, the American Society of Clinical Oncology (ASCO) announced immunotherapy as the year's top cancer advance in its "*Clinical Cancer Advances 2016: ASCO's Annual Report on Progress Against Cancer*." Further, ASCO again named "Immunotherapy 2.0" as the 2017 advance of the year, emphasizing the recent, rapid pace of research into new agents that harness and enhance the innate abilities of the immune system to recognize and fight cancers—and stressing that such agents have extended the lives of many patients with late-stage cancers for which there have been few treatment options. This article discusses the history of cancer immunotherapy and the recent promising advances, yet also presents a note of caution on limitations of immunotherapies, their potential harms, and the critical need for oncologists to appropriately engage with and educate patients to effectively manage their expectations.

Recent Findings Learning how to effectively harness the immune system to treat cancer represents an investigative journey of more than 100 years. However, after many failures and disappointments, this decade has seen several important successes. In 2011, the Food and Drug Administration (FDA) approved the first immunotherapy agent known as a "checkpoint inhibitor." Beginning in 2014, several additional checkpoint blockage drugs have been FDA-approved, and new indications and drug combinations have emerged. Further, on August 30, 2017, the FDA announced its first approval of a new form of immunotherapy known as CAR T cell therapy. Since the 2011 approval of the first checkpoint inhibitor, cancer immunotherapy research among the pharmaceutical industry and research institutions has exploded, with thousands of clinical trials currently taking place. The current "cancer immunotherapy revolution" is in the headlines daily and is also the primary topic of conversation among major cancer research conferences and symposia attendees. However, a once quiet voice has begun to emerge, where an increasing number of scientists, clinicians, and patient advocates are stressing the need for caution concerning the limitations and potential harms associated with cancer immunotherapy.

Summary Many oncologists, scientists, medical professional associations, and advocates agree that no recent cancer advance has been as successful, transformative, and potentially paradigm-shifting as immunotherapy. With this decade, we have seen the approval of several immunotherapy agents that have successfully treated a percentage of patients with notoriously resistant cancers, an increasing number of combination immunotherapy treatments, and new indications for approved agents. However, patients need to be aware that much of the popular media has breathlessly inflated positive outcomes of cancer immunotherapies, while neglecting to stress that just a small percentage of patients actually benefit from such treatments. Further, they often completely overlook the unique, potentially life-threatening harms that may be associated with these agents and fail to cover negative findings where immunotherapies have appeared to paradoxically accelerate cancer growth. Fortunately, the majority of journal articles presenting trial results and comprehensive review articles appropriately discuss the important limitations associated with immunotherapies, the unique spectrum of adverse effects, and the need for further research to improve our ability to identify those patients who are most likely to benefit from specific agents, sparing other patients from exposure to agents that will not be effective, yet may carry potentially life-threatening toxicities.

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Introduction

After more than a century of disappointments, the wind seems to have shifted thanks to a series of successes that have now been reported for a large number of human cancers, including melanoma, lung cancer, bladder cancer, head and neck cancers, kidney cancer, leukemia, and Hodgkin's lymphoma. To understand much of the excitement that is currently surrounding immunotherapy, it is important to look back at the history of its development. Back in 1891, a New York orthopedic surgeon, Dr. William Coley, who is now often called the "Father of Immunotherapy," found reported cases where patients' sarcomas appeared to spontaneously regress after they had developed a postoperative skin infection caused by strep bacteria (erysipelas). Coley developed an early immunotherapy using bacterial toxins, theorizing that the toxins would stimulate phagocytes, the antibacterial white blood cells that engulf, absorb, and break down bacteria, also potentially killing invading tumor cells. Although there were some successes over the next several decades with this approach, they were sporadic and difficult to reproduce [1, 2, 3]. There was one important exception, where following surgery for bladder cancer, injection of a live weakened version of BCG, the bacterium that causes tuberculosis [4, 5], prolonged patient survival and is still being used today—suggesting that BCG may have worked similarly to Coley's toxins by boosting cellular immune response against cancer by triggering one against the bacterium. Yet other than for this specific medical setting, oncologists failed to embrace Coley's strategy due to concerns about the potential harms associated with administering infectious agents to cancer patients with already comprised immune systems and the treatment's lack of predictability [3]. Further, little was known about the immune system in the scientific community at that time. Therefore, no one understood the mechanism of action with Coley's approach and why and how it was effective in some cases yet not in many others. Rather, oncologists continued with surgical methods and new approaches that were increasingly found to be effective and much more predictable in treating cancer, including radiotherapy and chemotherapy.

Further Progress in Immunotherapy—and the Introduction of Hype

In 1957, cancer immunotherapy again garnered the spotlight when both Drs. Macfarlane Burnet [6••,7] and Lewis Thomas [7, 8••, 9••] proposed a theory known as immunosurveillance, suggesting that the immune system has a monitoring process through which immune cells recognize and destroy foreign pathogens and cells that have become cancerous through spontaneous mutations. However, the absence of data and the lack of technical ability to perform the necessary cultures in vitro again postponed the emergence of immunotherapy as viable treatment for cancer [1].

Thus, for much of the last century, progress in treating cancer did come primarily from radiation therapy and chemotherapy. However, solid tumors that have spread from the initial site, such as lung cancers, often remained resistant to treatment. In 1966, tumor immunologist Dr. Herbert Oettgen, Dr. Lloyd Old, and colleagues [10] discovered antibodies to the Epstein-Barr virus in patients with nasopharyngeal cancer, suggesting the role of Epstein-Barr in causing the disease. In the early 1970s, when the Nixon administration declared America's "war on cancer," many scientists theorized that cancers resulted from viruses, and many thought that interferon, a commercially developed antiviral protein, may represent a potential cure. In fact, in 1980, interferon appeared on the cover of *Time* magazine [11], where the magazine reported: "The drug companies know that there is a gold mine in interferon. They are scrambling like mad to produce it." However, the reality was that although interferon was shown to shrink tumors in mice, the agent failed to cure patients with solid tumors and only occasionally was beneficial for melanomas. Unfortunately, *Time*'s cover story was one of the first examples in a long parade throughout the years, where the benefit of novel cancer therapies was hyped by the mass media, inflating the general public's expectations for a "cancer cure."

Although interferon proved a crushing disappointment, it did have the effect of revitalizing research into comparable molecular agents produced by the body that could be modified to enhance efficacy. Over the next decade, additional proteins produced by the body's immune response were developed into drugs, most notably interleukin-2. Made by a type of T lymphocyte, interleukin-2 is a natural immune system booster that increases the activity and growth of other T lymphocytes and B lymphocytes. The treatments are produced in the laboratory, using this protein to transform a patient's white blood cells into activated tumor-killing cells: i.e., interleukin-2 is a biological response modifier that can boost the immune system as a cancer therapy. Once again, it was touted by some as a potential cure for cancer. However, most solid tumors did

not respond, the therapy was extremely expensive, and treatment caused severe adverse effects for a significant percentage of patients. Yet it did receive FDA approval for the treatment of the "immunologic cancers" melanoma and renal cell carcinoma.

Monoclonal Antibodies, Targeted Agents, and Cancer Vaccines

In the 1970s, Drs. Georges Kohler and Cesar Milstein, who later received the Nobel Prize in Medicine [12] for their invention, produced mouse monoclonal antibodies (mAbs) through hybridoma technology in the laboratory, where antibody-secreting cell lines were formed by fusing lymphocytes with myeloma cell lines [1,13••, 14]. With this technology, scientists are able to mass-produce antibodies that target specific components of cancer cells. For example, such research led to the development of rituximab, a monoclonal antibody that binds to CD20 on the surface of B cells, targeting them for elimination by natural killer cells. Monoclonal antibodies now form a crucial part of our cancer treatment armentorium.

Further, in the past two decades or so, researchers found that tumors contain genetic mutations that result in cancer's uncontrolled growth, leading to the development of novel agents that target specific genes and proteins. The first successful targeted therapy was imatinib [3, 15], a tyrosine kinase inhibitor that targets a protein generated by a specific chromosomal abnormality in patients with chronic myelogenous leukemia. Imatinib now has also been approved for several forms of gastrointestinal tumors. Another important example is trastuzumab [3, 16], a monoclonal antibody that targets HER2, a protein receptor on the surface of tumor cells. Overexpression of HER2 in patients with HER2+ breast cancer leads to activation of multiple signaling pathways, resulting in increased, uncontrolled tumor cell growth. HER2+ cancers tend to have a more aggressive course with an increased risk of metastasis when compared with other breast cancer types. Yet the treatment of HER2+ breast cancers has significantly improved with the development of trastuzumab and additional anti-HER2-targeted therapies, including pertuzumab. Many targeted therapies are considered standard of care for different cancer types and are often used together with surgery, chemotherapy, and/or radiation therapy. However, despite such crucial progress in understanding the molecular biology, pathways, and targets in different cancer types and our ability to directly target mutations that cause tumor proliferation, there remain significant limitations and challenges [17]. Namely, resistance ultimately develops to molecularly targeted therapies due to cancer's ability to activate alternative signaling pathways, overcoming the target agent's blockage. Therefore, once again, the hype surrounding these targeted therapies must be balanced with realistic expectations due to treatment efficacy for only a percentage of patients with such "actionable" mutations as well as the ultimate development of resistance [17].

And what about cancer vaccines? In contrast to preventive vaccines that are primarily given to healthy people, therapeutic cancer vaccines are designed to attack tumor cells through strengthening patients' own immune responses to specifically target and destroy cancer cells while sparing normal cells. The hope has been that therapeutic cancer vaccines may be used to inhibit further progression of late-stage cancers or relapsed cancers refractory to more standard treatments. Although developing effective therapeutic cancer vaccines has challenged researchers for decades, two preventive vaccines have been approved by the FDA, including for hepatitis B virus that causes liver cancer (in 1981) and the human papillomavirus that causes the majority of cervical cancers (in 2006) [3, 18, 19].

With more recent advances, in 2010, the first immune cell-based therapeutic vaccine led to increased overall survival for men with progressive castration-resistant prostate cancer. Called sipuleucel-T (Provenge®), the vaccine is produced by culturing a patient's immune cells with a recombinant antigen. When infused back into the patient, it triggers the immune system to produce T cells that recognize and attack prostate cancer cells. Clinical trial results showed that the vaccine extended overall survival by 4.1 months, but did not have any effect on time to disease progression and did not shrink the primary tumor nor metastases. Its FDA approval was extremely controversial, where skepticism remains regarding key trial data, with some questioning whether there was an age bias, since only men aged 65 years and older were benefiting, and whether the placebo intervention was actually harmful, making the treatment intervention appear better by comparison [3, 20]. Further, as an essentially personalized vaccine, it carried a cost of $93,000 for the required three courses of treatment [21]. Though there are continued challenges associated with developing efficacious therapeutic cancer vaccines, several different therapeutic vaccination strategies continue to be studied in clinical trials or are under development [3, 18, 19]. Unfortunately, however, many unproven vaccines repeatedly gain headlines, being heralded as "dramatic breakthroughs" or "game changers," despite the fact that many may not have reached large-scale phase III clinical trials or where investigators may have conducted unplanned, post-hoc analyses in an attempt to show potential benefit despite negative results [22, 23, 24••, 25]. As Dr. J. Leonard Lichtenfeld, deputy chief medical officer of the American Cancer Society, blogged in 2008 [22], "There is something that fascinates the public about the possibility of treating cancer with a vaccine. Perhaps that explains why so many abstracts and journal articles about the latest cancer vaccine research find their way into our newspapers, magazines, and television reports."

CAR T Cell Therapy and Immune Checkpoint Inhibitors

Just last year, tisagenlecleucel (Kymriah®) became the first FDA-approved gene-modified cell therapy [26] called adoptive cell transfer (ACT); this rapidly emerging form of immunotherapy involves obtaining and using a patient's own immune cells to treat cancer. Though there are different forms of ACT [18, 19], tisagenlecleucel is known as a CAR T cell therapy. This individualized therapy requires removing T cells from the patient's blood and sending them to a specialized center where the cells are engineered to express a chimeric antigen receptor (CAR). They are then infused back into the patient, helping the altered T cells to locate and attack the CD19 antigen located on malignant B cells. Tisagenlecleucel was approved by the FDA for children and young adults with relapsing B cell acute lymphoblastic leukemia (ALL), based on clinical trial results reporting 83% remission rate in patients who have not responded to standard therapies. Though there is a great deal of enthusiasm concerning such remarkable responses, it is critical that its limitations and potential harms do not get lost in translation. Importantly, CAR T cell therapy can cause cytokine release syndrome (CRS), which can cause life-threatening complications, including rapid onset of dangerously high fever, flu-like symptoms, cardiac dysfunction, acute respiratory distress, or multi-organ failure. Further, as with other forms of immunotherapy, ACT may not prove to effectively treat solid tumors. In addition, such therapy comes with an extremely high financial cost: $475,000 for a single infusion [3, 27].

And then there are the immune checkpoint inhibitors. This new class of agents has captured and held onto the spotlight over the last few years, generating a great deal of excitement among oncologists, investigators, academia, industry, advocates, patients, and the overall public alike. The research community's growing knowledge concerning the interactions between cancer cells and the tumor microenvironment was vital in leading to the development of checkpoint inhibitors. We know now that T cells are constantly patrolling for signs of disease or infection, identifying cells by probing specific proteins on the cellular surface. If the proteins suggest that the cell is cancerous or infected, the T cells will begin to attack—and the immune system increases checkpoint molecules, which have been described as a form of "off switch" or negative regulator that puts the brakes on overactivation of T cells, preventing them from going into overdrive and attacking other normal, healthy cells.

To evade detection and elimination by the immune system, cancerous cells frequently exploit these checkpoint pathways, sending deceptive signals at particular checkpoints that trick adaptive T cells into not finding the cancer cells harmful. Checkpoint inhibitor agents are designed to disrupt the tumor cells' signaling by inhibiting the checkpoint, thereby releasing the brakes on the immune system, overcoming the cancerous cells' evasive measures, and exposing them to attack by the T cells.

The first checkpoint inhibitor was approved by the FDA in 2011 for the treatment of advanced or unresectable malignant melanoma based on results of a trial that showed a significant survival benefit in patients with stage III or IV melanoma. Called ipilimumab [3, 18, 19, 28••], the agent is a monoclonal antibody that targets cytotoxic T lymphocyte-associated protein 4 (CTLA-4), which is a gene that limits the ability of T cells to mount an attack against cancer cells. Following a pause of 3 years, multiple new checkpoint inhibitors were approved by the FDA in 2014 that similarly enable the immune system to reactivate against cancerous cells, targeting and inhibiting the programmed death 1 (PD1) and programmed death ligant 1 (PD-L1) braking system. Such agents include pembrolizumab, nivolumab [29], avelumab, atezolizumab, and durvalumab [28••, 30••] and have been approved for multiple cancers, including Hodgkin's lymphoma and, importantly, several advanced solid tumors, including advanced or unresectable malignant melanoma, non-small-cell lung cancer, metastatic renal cell carcinoma, head and neck cancer, and locally advanced or metastatic urothelial cancer.

Yet what has been described as the "checkpoint immunotherapy revolution" has brought with it significant concerns that often are getting lost in the media storm. And despite the optimism, it is critical to note that, once again, this is still "early days," and the evidence is still emerging. As a cancer research advocate, my role includes focusing on the current state of the evidence; ensuring that medical and scientific information is presented transparently and realistically; and cautioning against inappropriately raising the hopes of patients with advanced cancers when the data is still in its infancy. Said another way, because the encouraging results for a small percentage of patients with advanced, previously resistant disease have been so widely trumpeted and because critical research continues, it is crucial that cancer patients are provided with clear, accurate, balanced information on what to expect from immunotherapy, including its very real limitations. It is the responsibility of our oncology providers as well as anyone who is writing and publishing scientific information on immunotherapies, regardless of the forum—journal articles, other scientific publications, mass media, etc.— to clearly, transparently discuss the critical considerations outlined below.

First, immunotherapy is not for every patient. Patients who have received organ transplantation and/or have a history of liver damage are not considered appropriate candidates. Because such treatment enhances immune responses and thus can also inflame healthy, normal tissues, many clinicians are reluctant to use such treatments for patients with autoimmune diseases. Further, such patients have largely been excluded from immunotherapy clinical trials due to their autoimmune

comorbidities. However, case reports and retrospective reviews have demonstrated evidence of efficacy, safety, and tolerability with checkpoint inhibitors for patients with autoimmune conditions—despite a significant percentage receiving immunosuppressant therapy at their treatment initiation and experiencing exacerbations of their autoimmune disease. Therefore, it is critical that clinicians engage in informed discussions with their patients about whether they are appropriate candidates for checkpoint inhibitor therapy, thoroughly weighing the potential benefits and harms and discussing the need for carefully monitoring for autoimmune side effects [31].

Any patient receiving checkpoint inhibitors may develop a unique spectrum of autoimmune side effects known as immune-related adverse events (irAEs), since the enhanced immune responses and inflammatory reactions with checkpoint inhibition may also impact healthy cells and tissues. It is therefore unfortunate that many reports in the popular media have suggested that such therapy "typically results in fewer side effects that are less severe" than those associated with other forms of cancer treatment, e.g., chemotherapy. This is extremely misleading for patients, since when irAEs occur, they can be serious or potentially life-threatening. They may comprise inflammation of any organ system and, unlike with most standard cancer therapies, they may tend to be delayed, with onset weeks to months following treatment initiation or after therapy completion. It is critical for patients to be made aware of irAEs before initiating treatment, when they may develop, and the importance of reporting such symptoms, no matter how subtle or "minor," to ensure prompt evaluation for determining whether an irAE has developed and rapid initiation of appropriate treatment [32, 33].

Another critical point often is not even mentioned by the popular media: currently, only a small percentage of patients have what is often described as remarkably beneficial responses [2, 28••, 34]. As co-authors, Nathan Gay and Vinay Prasad, noted in their March 8, 2017 editorial aptly entitled "Few people actually benefit from 'breakthrough' cancer immunotherapy," they stressed that "When immunotherapy works, the result is terrific, even life-changing. Today, though, only a tiny minority of patients expected to die from cancer will benefit from immunotherapy. As is often the case, hype sadly exceeds evidence, creating misunderstandings between patients and their doctors." [34] Based on the percent of cancers for which checkpoint inhibitor therapies had been approved by February 2017 and the United States National Cancer Statistics, the authors estimated that, assuming patients could afford these expensive therapies and obtain access, only 8% of cancer patients would benefit [34].

Research has found that cancer types with a high number of mutations, such as malignant melanoma and lung cancer, tend to respond much more effectively to checkpoint inhibitors than tumors with fewer mutations. Those with strong responses tend to have large numbers of neoantigens—mutations producing molecules that move to the cancer cell surface—or a lower number of neoantigens that are expressed in nearly all cancer cells—enabling T cells to recognize and attack the foreign proteins [35, 36]. Tumors with mismatch repair deficiency and associated genomic instability also tend to be more responsive to checkpoint inhibition. It is therefore critical that patients receive an accurate picture regarding the small percentage of responders and understand that the immunotherapy field is a rapidly developing one, with hundreds of combination immunotherapy trials taking place for different cancer indications.

Thus, the next important step is developing robust methods to accurately predict toxicity and efficacy to determine which patients are most likely to benefit from these potentially toxic and expensive therapies. Research efforts are ongoing to identify effective, reliable biomarkers of response, yet validating such biomarkers continues to present a challenge due to variability of protein expression during a cancer's course and tumor heterogeneity.

Patients must also understand that for those who do benefit, the time to and the nature of such response is also variable. Rarely, palpable tumors may decrease in size in just days. Yet response is more typically apparent a few months after beginning therapy. Patients should also be made aware of the possibility of "pseudo-progression"—where a tumor may first appear to become larger due to immune cell tumor infiltration—followed by a decrease in tumor burden [37, 38]. To further muddy the waters, the response to checkpoint inhibitors may appear ambiguous. Some patients may have improvement in multiple cancerous areas, yet simultaneously develop new lesions. With more traditional treatments, increased tumor burden is associated with cancer progression; therefore, again, patient education is a key part of setting proper expectations [32, 33, 37].

As work continues to discover biomarkers to predict response, greater is their promise for a growing number of patients. Yet patients should be made aware that checkpoint inhibition is not likely to replace efficacious chemotherapy regimens, radiation, and targeted therapies for many cancers [2]. Rather, optimal benefit will probably result from combination therapies, e.g., combination checkpoint inhibition; combining immunotherapy with targeted therapy for a potential synergistic response; or combined radiotherapy and checkpoint inhibition, where research suggests that the former strengthens T cell recruitment and function [39, 40]. Importantly, further research is also critical concerning optimal timing, sequencing, and possible increased toxicities with combination therapies [39, 40].

There have also been recent studies reporting cases where PD-1 checkpoint inhibitors parodoxically appeared to cause rapidly accelerated cancer growth and early death [41, 42]. Measuring tumor growth is complex and can be imprecise. In addition, the reported studies are small. But very few

journalists covered these study results, and it is concerning that is so often the case with negative findings. While many in the medical community feel the potential benefits of the checkpoint inhibitors outweigh what is currently anecdotal evidence, there is agreement that further research is critical to confirm or refute these results. This is yet another example of where publication bias is harmful should it ultimately prevent the conduct of research to robustly answer such critical questions.

Conclusions

There is no denying that cancer immunotherapy has made remarkable strides in the last century and that the introduction of checkpoint inhibitors and ACT may in fact represent a paradigm shift. Yet we all must acknowledge that many more questions than answers remain. It is therefore crucial to wash away the hype, present the medical data transparently to patients and in any publications, and promote continued research to obtain the mature data and robust evidence base required regarding safety, efficacy, tolerability, appropriate patient selection, durability of response, and overall impact on patients' length and quality of life.

Compliance with Ethical Standards

Conflict of Interest Debra L. Madden was a speaker at the *American Journal of Managed Care* (*AJMC*)'s 5th Annual Patient-Centered Oncology Care meeting, where she gave a presentation from the perspective of a cancer research advocate and cancer survivor called "Immunotherapy: The Promise, the Challenge, and the Patient." The *AJMC* covered all travel expenses and issued an honorarium as well. She has also served as a contributor to their website and blogged there with the same focus, but has received no compensation for her blog contributions. She also writes her own blog entitled "Musings of a Cancer Research Advocate," from which she linked to her *AJMC* contributions, but has received no compensation for writing her blog.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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