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REVIEW

Cancer Immunotherapy: A Simple Guide for Interventional Radiologists of New Therapeutic Approaches

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Abstract The therapeutic options in the treatment of cancer therapy have been recently significantly increased with systemic immune-targeted therapies. Novel immunotherapy approaches based on immune checkpoint blockade or engineered cytotoxic T lymphocytes have reached late-stage clinical development, with highly encouraging results. The success of cancer immunotherapy has generated a tremendous interest in further developing and exploring these strategies in combination with other approaches such as radiotherapy and local ablative therapies in oncology. The goal of this review is to discuss current approaches in immunotherapy and provide simple and constructive explanations on their mechanisms of action as well as certain more common and serious toxicities.

Keywords Cancer · Immunotherapy · Interventional radiology

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Introduction

Since 1891 when Dr. William B. Coley developed the first immunotherapy approach in sarcoma patients by inoculating bacteria that stimulated a sustained antitumor immune response, stimulation of the immune system alone has not been shown to have any clinical benefit [1, 2]. After decades of research and development, this has changed with the approval of ipilimumab, the first checkpoint inhibitor approved for the treatment of melanoma [3]. In the last 5 years, research in cancer immunotherapy has significantly accelerated with new clinical applications [4] and has been highlighted at the American Society of Clinical Oncology (ASCO) for 2 years in a row. Immune checkpoint blockade, therapeutic cancer vaccines and engineered cytotoxic T lymphocytes offer novel alternative treatment options for solid tumors and hematological cancers.

What exactly is so exciting about immunotherapy to make the scientific community discuss a new era in the treatment of cancer? For the first time, patients with advanced cancer can achieve long-term survival and in some cases, we can go as far as to say that we are close to "curing" cancer [5]. Thus, immunotherapy is here to stay.

In this review, we will summarize the mechanisms of action of different immunotherapies and review the indication of these treatments and their toxicity profile (Table 1).

Immune System and Cancer

The immune system engages in a complex balance of identification and eradication of foreign antigens, counterbalanced by processes to suppress an uncontrolled immune response [6].

Table 1 Main characteristics of new immunotherapy class

Immunotherapy class	Molecule examples	Simplified mechanism of action	Specific class toxicities
Checkpoint inhibitors	Nivolumab	Human monoclonal antibody that blocks the interaction between PD-1, PD-L1 and PD-L2	Immune-mediated Pneumonitis, Colitis,Hepatitis, Hypothyroidism and Hyperthyroidism
Oncolytic virotherapy	Talimogene laherparepvec (T-VEC)	Genetically modified herpes simplex virus type 1 to recognize, infect and selectively destroy malignant cells	Fatigue, chills, nausea, pain at the injection site and headache
CAR T-cell therapy	Tisagenlecleucel	Reprogrammed autologous T cells to detect and destroy cancerous cells expressing certain antigen	High fever, flu-like symptoms, neurological toxicities
Tumor-infiltrating lymphocytes		Reinfusion of multiplied autologous T lymphocytes activated against antigens expressed in tumor cells	Fever, hypotension, pulmonary fluid overload, neurotoxicity and rarely capillary leak syndrome
Cancer vaccines	Sipuleusel-T	Activates cytotoxic T cells and directing them to recognize and act against cancer cells	Pain site of injection, chills, fever, headache

The major player cells are antigen-presenting cells (APCs) and CD8 + effector T cells, or cytotoxic T cells. Cytotoxic T cells recognize "self" and "non-self" antigens bound to major histocompatibility class I complexes that are expressed on APCs [7]. Cancer cells have undergone significant changes from genetic mutations/aberrations resulting in the production of neo-antigens (expression of proteins that are not normally expressed). Host defenses usually recognize these neo-antigens as "non-self," resulting in the production of cytotoxic T cells that can identify these neo-antigen-presenting cells and eliminate them. This concept of the immunological surveillance of cancer was described by Lewis Thomas and Frank Macfarlane Burnet more than five decades ago [6].

However, cancer cells can escape from immune recognition and response by several mechanisms, including local secretion of immunosuppressive cytokines, such as transforming growth factor β (TGF-β) and interleukin 10 (IL-10) as well as downregulation of surface major histocompatibility complex (MHC) class I molecules [8].

Over the last few decades, several approaches based on stimulation of the immune response have failed to provide any clinical benefit. However, a new era in cancer therapy began with the blockage of the inhibitory signaling pathways of the immune system (or so-called checkpoint inhibitors CPIs) which was shown to provide a significant benefit against different solid tumors [9].

Checkpoint Inhibitors (CPIs)

CPIs inhibit crucial regulatory steps of activation and proliferation of T cells. Releasing the brake on the immune system through negative regulation of T-cell-mediated antitumor immune responses is a critical step that controls both the duration and intensity of an immune response.

Three main types of CPIs have been studied thus far and obtained US Food and Drug Administration (FDA) approval: Cytotoxic T lymphocyte antigen-4 (CTLA-4) antibodies, programmed cell death (PD-1) and programmed cell death ligand (PD-L1 and PD-L2) antibodies. Recently, Hickey et al. provide a detailed explanation of existing information on the mechanism of action in this journal [10] (Fig. 1).

CTLA-4 is a molecule that downregulates T-cell responses and APC function, resulting in a decreased immune response to tumor-associated antigens (TAAs) and immune tolerance. T-cell activation is initiated by the binding of the B7 molecule on the APC to the CD28 T-cell receptor. CTLA-4 inhibition by monoclonal antibodies such as ipilimumab restores T-cell proliferation and results in amplification of T-cell-mediated immunity [11]. Currently, ipilimumab (Yervoy^{TM}) has received FDA approval for four doses at 3-week intervals for advanced melanoma [12].

Programmed-death-1 (PD-1) and programmed-death-2 (PD-2) are inhibitory cell surface receptors expressed on T cells, B cells, dendritic cells (DCs), macrophages and natural killer (NK) cells that promote self-tolerance by suppressing T-cell activation [13]. Once PD-L1 or PD-L2 ligands are bound in the PD-1 receptor, the inhibitory pathway is activated leading to T-cell suppression. Current data show that tumor expression of PD-L1 and T-cell expression of PD-1 is correlated to tumor aggressiveness and a poor clinical outcome in several tumors [14–16].

Nivolumab (Opdivo^{TM}) and pembrolizumab (Keytruda^{TM}) are PD-1 antibodies that have received FDA approval in multiple cancer types including metastatic melanoma, advanced non-small cell lung cancer (NSCLC),

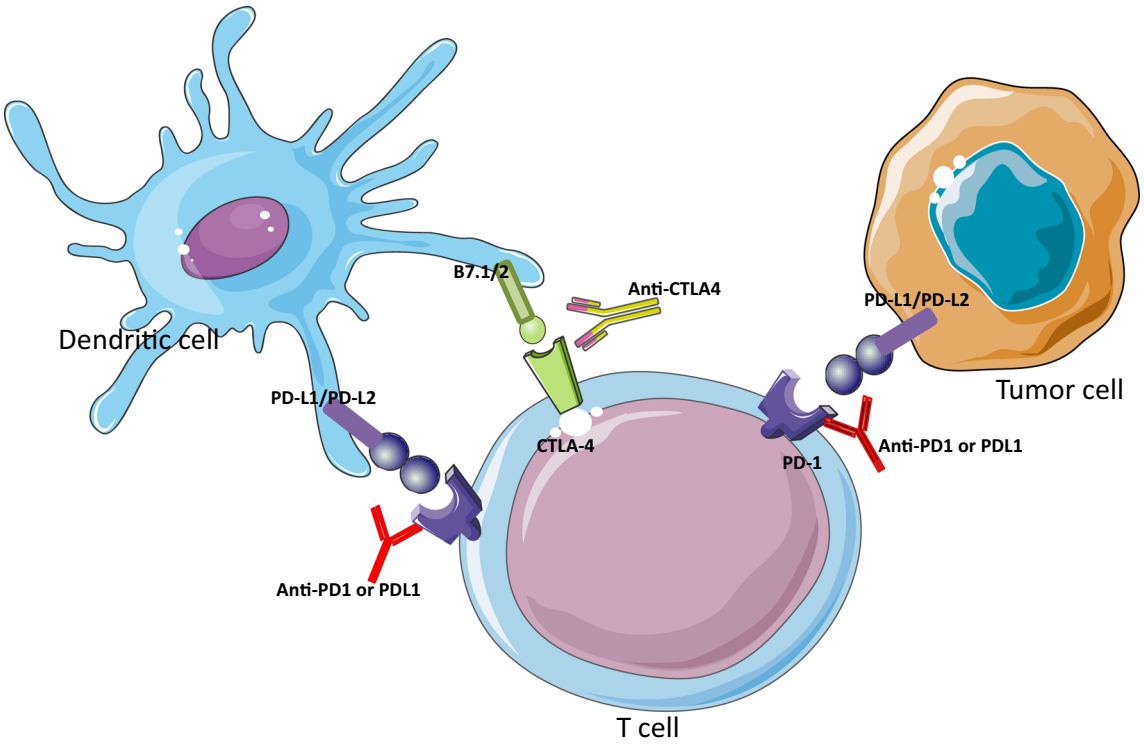

Fig. 1 Mechanism of action of anti-CTLA4 and anti-PD1 ou PDL1. Anti-CTLA4 binds to CTLA4 receptor. B7 molecules enable to bind to CTLA-4 receptor, preventing the suppression of cytotoxic T-cell function that would normally occur. PDL1/2 are expressed both on tumor cells and on antigen-presenting cells (ex-macrophage or dendritic cells). The expression of PD-1 ligands by tumor cells enables PD-1/PD-L1/L2 pathway to regulate T-cell responses locally in tumors, protecting them from immune attack. Like this, anti-PD-1/L1/L2 mAbs restore the immune response in early T-cell priming (APC–T-cell interaction) as well as in a later time point (tumor cell–T-cell interaction)

RCC and Hodgkin's disease [17–19]. Although it is more toxic, the combination of ipilimumab and nivolumab has resulted in improved three-year progression-free survival (PFS) in patients with metastatic melanoma than either nivolumab or ipilimumab alone (58 vs. 52 vs. 34%, respectively). Even though this trial was not powered to determine a benefit to OS in the combination compared to nivolumab alone, this combination is now the new standard of care in patients with good performance status [20].

Atezolizumab (Tecentiq^{TM}) is the first FDA-approved antibody that blocks the PD-1 ligand [21]. Inhibition of PD-L1 can remove the inhibitory effect and create an antitumor response. This treatment has been approved for locally advanced or metastatic urothelial carcinoma and metastatic NSCLC patients who have progressed with frontline chemotherapy [22, 23]. Other PD-L1 inhibitors are durvalumab and avelumab [24].

Other promising inhibitors of immune checkpoint targets using blocking antibodies under clinical study include the lymphocyte-activation gene 3 (LAG-3), the T-cell immunoglobulin and mucin domain 3 (TIM-3) [25]. There are several ongoing clinical trials to evaluate their clinical effect in monotherapy or in combination with other checkpoint inhibitors.

As CPIs are more extensively used, it is highly important to be aware of the unique toxicities of these treatments, which are distinct from those seen with traditional chemotherapies. Immune-related adverse events (AE) are the most common events and usually occur within the first 3 months of therapy, but delayed events may also occur as long as 1 year or more after treatment begins. Patients treated with the combination of CTLA4 and PD1/PDL1 blockade develop more AEs than those who receive with monotherapy (about 95% of the patients with half $\geq$ grade 3 compared to 70% and 25%, respectively). AEs also occur earlier than with monotherapy. Immune-related colitis and skin toxicity (rash, vitiligo) are the most common elevated aspartate aminotransferase or alanine aminotransferase, endocrine immune-related adverse events (thyroid dysfunction, hypophysitis) and pneumonitis. These events are managed according to the severity (grade) of toxicity.

Toll-Like Receptors (TLRs)

Toll-like receptors (TLRs) play a key role in the detection of "non-self" particles, in particular a wide range of infectious agents and are therefore fundamental in the activation of innate, as well as adaptive, immunity. Intratumoral inoculation of the TLR agonists, bacillus Calmette–Guerin (BCG) and imiquimod has been approved by the US FDA for certain tumors. However, systemic immune activation by TLR agonist monotherapies is generally insufficient thus they could best serve as adjuncts or adjuvants to other immune modulatory therapies. Novel TLR agonists such as CpG or motolimod (VTX2337) are being evaluated in combination with immune CPIs, with the hope that local TLR activation will have an abscopal effect at other tumor sites resulting in synergistic tumor control. Furthermore, intratumoral injection of TLRs alone or in combination with co-stimulatory molecules (such as OX40) is being studied to determine whether this combination can provide a robust local and systemic antitumor immune response (NCT03410901).

Oncolytic Virotherapy (OVs)

Oncolytic virotherapy is an exciting new area of cancer treatment. It is based on the ability of a virus to selectively replicate and cause cancer cell death through several mechanisms including hijacking of cellular death pathways, and promotion of cellular immunity. A wide variety of parental viruses has been used for these strategies, including adenoviruses, herpes simplex virus type 1 (HSV-1) and Sendai virus (HVJ) [26]. Since 1996, several clinical oncolytic virus trials have been started and H101 was the first virus to receive marketing approval. This oncolytic adenovirus was approved by the Chinese FDA in 2006 for the treatment of squamous cell cancers of the head and neck or esophagus in combination with cisplatin-based chemotherapy (in Chinese, only abstract available https://www.ncbi.nlm.nih.gov/pubmed/15601557).

Talimogene laherparepvec (T-VEC) (Imlygic^{TM}) was the first oncolytic immunotherapy and the first intralesional immunotherapy to receive FDA approval in 2015 and then worldwide for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after primary surgery [27, 28]. This engineered oncolytic herpes simplex virus type 1 (HSV-1) is genetically modified to recognize, infect and selectively destroy malignant cells while activating the immune system by the coding sequence of the granulocyte–macrophage colony-stimulating factor (GM-CSF) for immunostimulation [29]. The common side effects of T-VEC are fatigue, chills, nausea, pain at the injection site and headache. Rare serious side effects include deep vein thrombosis, vasculitis, herpes virus infection and acute asthma.

There are several ongoing clinical trials to evaluate the intratumoral injection of T-VEC or another oncolytic virus (for example, intrahepatic, intrapancreatic, intraprostatic or into breast lesions) alone or in combination with checkpoint inhibitors (NCT02263508). Although the systemic delivery of oncolytic viruses is highly promising since it may help track tiny tumor lesions as well as circulating tumor cells, it is still limited by antibody and complement coating which causes sequestration and effects clearance in the liver and spleen. At present, one case of durable complete remission after a single systemic infusion has been reported suggesting that these physical barriers to tumor homing may be overcome by dose escalation [30].

Adoptive Cell Therapy (ACT)

ACT is a form of passive and personalized immunotherapy, which uses autologous cytotoxic T lymphocytes against cancer cells. Encouraging clinical benefits have been found with two main approaches: genetic modification of T cells with **c**himeric **a**ntigen **r**eceptors (CARs) and therapy with autologous tumor-infiltrating lymphocytes (TIL).

CAR T-Cell Therapy

T cells are natural eliminators and key players in the immune response which are usually exhausted in the tumor environment. There are several existing genetic approaches to reprogram circulating T cells to become highly specific cancer cell "killers." As shown in Fig. 2, with the help of a viral vector, autologous T cells are reprogrammed to "hunt" cancer cells that express specific proteins. These reprogrammed T cells are reintroduced into the patient's blood, where they proliferate, bind to the targeted "protein-positive" cancer cells and potentially kill the tumor cells. Results with this approach have been promising in haematological cancer and it is considered a breakthrough in this context [31, 32].

Kymriah^{TM} (tisagenlecleucel) and Yescarta^{TM} (axicabtagene ciloleucel) [33, 34] target antigen CD19, a protein expressed on the cell surface of B-cell lymphomas and leukemias. In the ELIANA trial, a single dose of Kymriah^{TM} resulted in an overall remission rate of 81% (52/63) in a pediatric or young adult population with heavily pretreated acute lymphoblastic leukemia (ALL). In a multicenter clinical trial of 101 adults with refractory or relapsed large B-cell lymphoma, 51% are presented with a complete remission after treatment with Yescarta^{TM}.

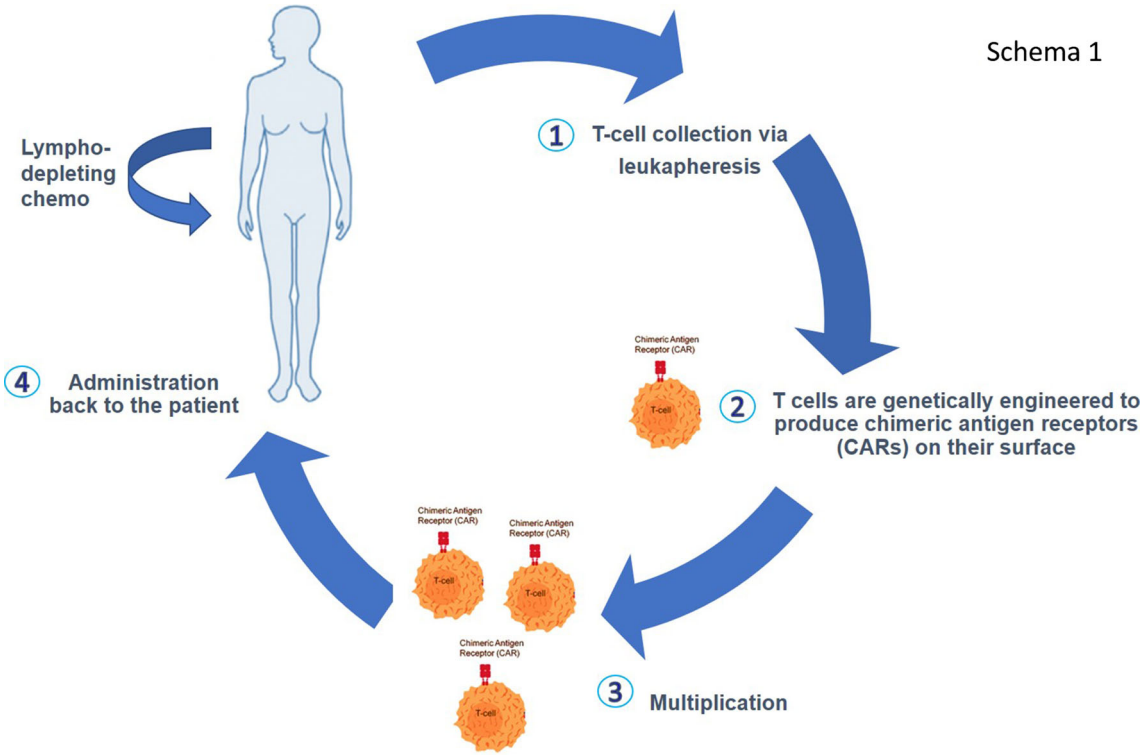

Fig. 2 Overview of CAR T-cell therapy. A patient's T cells are harvested through leukapheresis, followed by genetic manipulation ex vivo by transduction with a construct encoding the CAR. The "CAR T cells" are expanded and infused back into the patient, who has been preconditioned by lymphodepleting chemotherapy (in order to remove all suppressive influences)

This type of therapy has severe toxicities such as the cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T cells causing high fever and flu-like symptoms, as well as neurological toxicities [CAR T-cell-related encephalopathy syndrome (CRES)]. Both of these events can be fatal or life-threatening and must be managed by close observation, supportive care and (in some cases) intervention with steroids or cytokine receptor blockade medications [35]. Thus, these treatments can only be administered in certified centers.

In solid tumors, a recent phase I escalating dose trial was performed with CAR T-cell therapy targeting carcino-embryonic antigen (CEA)-positive metastatic colorectal cancer (CRC). Toxicity was favorable in this study and disease was stable in 7/10 patients. It is interesting to note that the disease remained stable in two patients for more than 30 weeks [36]. However, the problems to be overcome in solid tumors include a lack of known unique tumor-associated antigens (low specificity with a risk of side effects), inefficient homing of T cells to tumor sites and the immunosuppressive microenvironment of solid tumors (such as expression of PD-L1 and secretion of TGFβ). Several strategies are being evaluated to solve these problems such as genetic modifications to secrete anti-PD L1, to express the homing receptor (ex CXR2) as well as co-stimulatory ligands (ex CD40L).

Intratumoral injection of CAR T cells is an area of potential development since it could theoretically help overcome poor T-cell migration and avoid systemic toxicity. This approach has been shown to be feasible and safe based on results from the regional injection of CAR T cells in breast cancer patients, hepatic arterial infusion in colorectal patients with liver metastases and from intraventricular injection in glioblastoma patients. Proof of principle studies is ongoing and confirms that the role of interventional radiologists will be highly important in cancer as the use of these techniques is expanded.

Tumor-Infiltrating Lymphocytes (TIL)

Intratumoral lymphocyte infiltration is correlated with better survival in the metastatic stages of some solid tumors. TILs therapy is based on the clonal expansion in vitro of these T lymphocyte population targeted against antigens expressed in tumor cells, reconditioning them (e.g., cultured them with artificial APCs in the presence of cytokines) and then reinfusion in the host (Fig. 3). Patients need to have a lymphodepletion chemotherapy before reinfusion followed by IL-2 administration after reinfusion for immunostimulation.

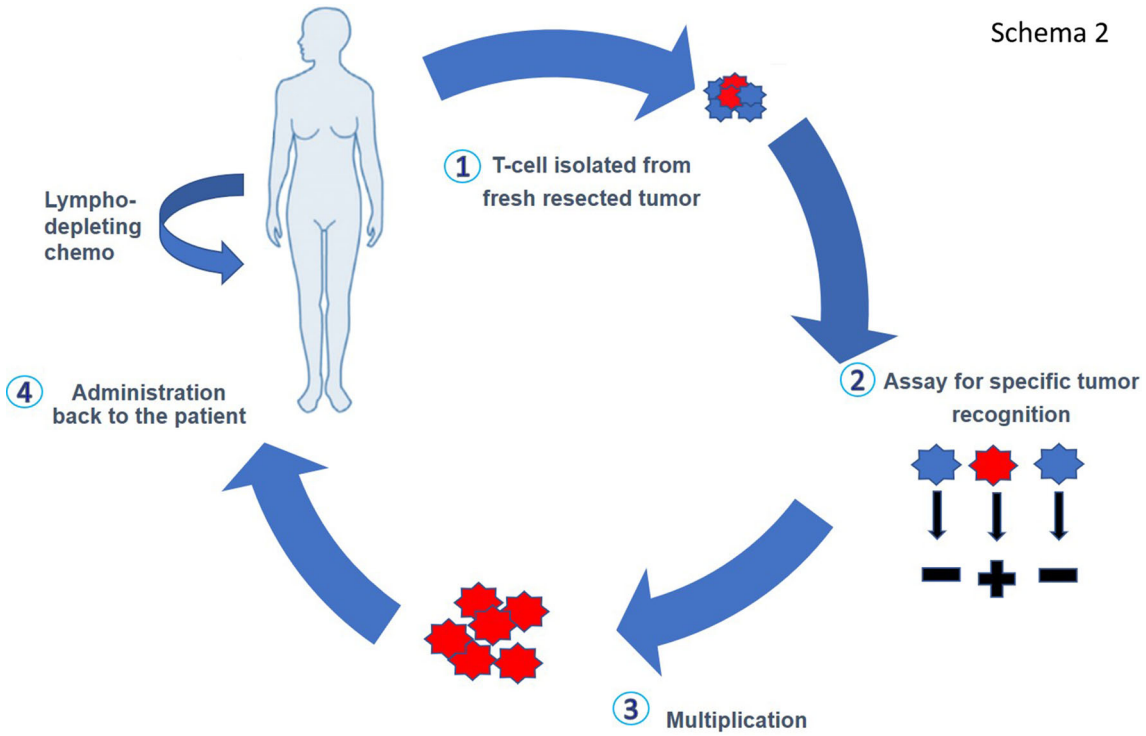

Fig. 3 Overview of autologous tumor infiltrating lymphocytes (TILs) therapy. A patient's TILs cells are isolated through tumors surgically resected, followed by their activation and expansion. The potent TILs are infused back into the patient, who has been preconditioned by lymphodepleting chemotherapy

Side effects are related to lymphodepletion chemotherapy before reinfusion as well as in the high dose IL-2. Cardiotoxicity, fever, hypotension, pulmonary fluid overload, neurotoxicity and rarely capillary leak syndrome are the most important, underlying the necessity of long-lasting hospitalization (3–4 weeks).

Limitations of this therapy are the need of adequate tumor mass in order to isolate TILs and that the duration of this procedure is 5–6 weeks. These mean that there a need for a selection of fit patients characterized with a non-aggressive disease.

Results of several small clinical trials are really encouraging with response rates 30–60% in melanoma heavily pre-treated population [37–39] and have demonstrated objective responses in other malignancies (cholangiocarcinoma) [40]. Currently, several trials are ongoing in different tumor types, alone or in combination with checkpoint inhibitors.

Cancer Vaccines

Therapeutic cancer vaccines hold great promise in the fight against cancer since they are designed to work by activating cytotoxic T cells and directing them to recognize and act against cancer cells or by inducing the production of antibodies that bind to molecules on the surface of cancer cells. There are several types of vaccine therapies, which are distinguished by how they are made. Two of the available ones are made by whole tumor cell lysate [41], or by dendritic cells either fused with tumor cells or loaded with tumor lysates. Figure 4 summarizes the underlying mechanism of action.

Although more than 15 vaccines are under clinical investigation in several trials for a range of cancers, including lymphoma, melanoma, breast, lung and colorectal cancers, currently the only approved vaccine-based therapy is sipuleusel-T (Provenge^{TM}) for men with castrate-resistant prostate adenocarcinoma [42]. This autologous dendritic cell preparation engineered to target prostatic acid phosphatase has demonstrated a benefit of 4.1-month improvement in median survival in a phase III trial (25.8 months in the sipuleucel-T group vs. 21.7 months in the placebo group) [43]. Adverse events that were more frequently reported in the sipuleucel-T group included chills, fever and headache.

Two recent phase I trials with personalized cancer vaccines targeting neo-antigens (using sequencing and computational identification) in melanoma patients have shown vaccine-induced T-cell infiltration and neo-antigen-specific killing leading to very interesting clinical activity, underlying the potential of this personalized approach

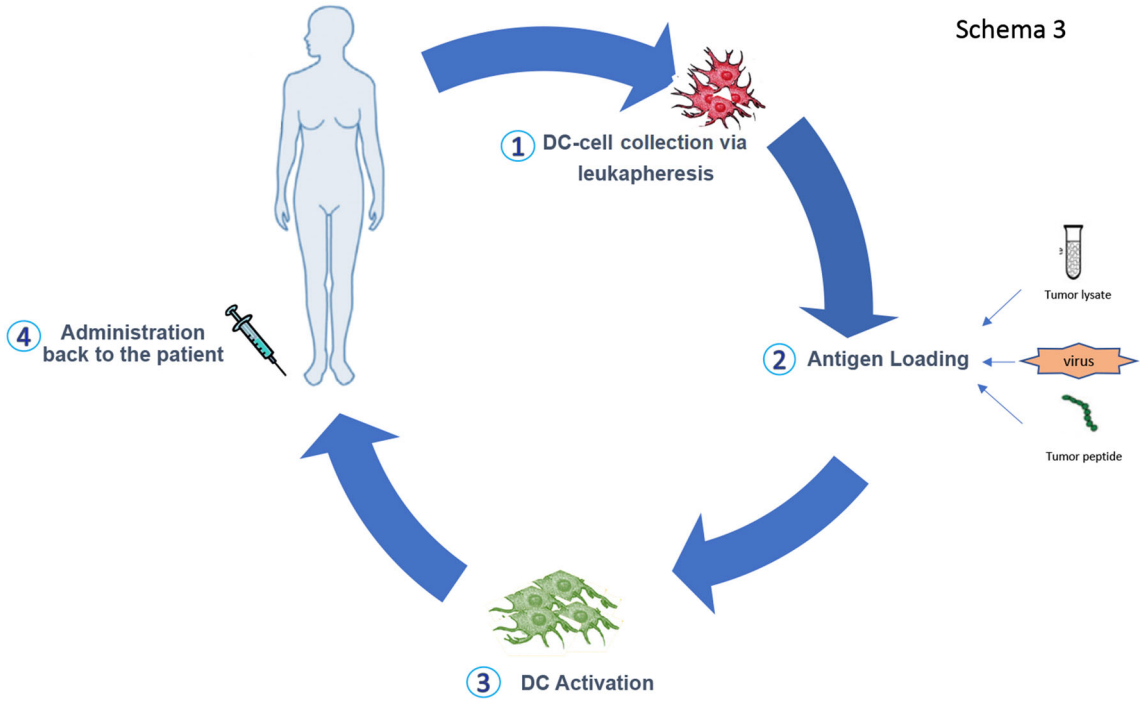

Fig. 4 Overview of Dendritic cell (DC) vaccines. A patient's DC cells are harvested through leukapheresis, followed by their activation and expansion in vitro. The potent DCs are infused back into the patient

[44, 45]. The most frequent reported side effects are skin reaction at the injection site (including redness, pain), pyrexia, flu-like symptoms and pyrexia.

Currently, there are several open questions; What is the best route of administration? Should it be systematic, intradermal, intratumoral or peri-draining lymph node injection in order to potentiate more antitumor effect? Which type of cancer vaccine is more immunogenic? Should we combine them with other anticancer therapies (for example, chemotherapy or CPIs)?

Role of Interventional Radiologist (IR) in the Era of Immunotherapy

The IR in immunotherapy era encompasses a wide-ranging role. IRs perform biopsies for both diagnostic reasons and translational research, for example, to help determine response of a predictive biomarkers in immunotherapy.

Currently, PD-L1 status has shown trends for increased response rates to PD-1 blockade in PD-L1 "positive" tumors. On the other hand, responses were also seen in PDL1 negative tumors in either retrospective or prospective assessments of PD-L1 status. In this context, the potential applicability of PD-L1 in different disease settings is still pending with probably the exception of first-line lung cancer. Other predictive biomarkers that have been explored retrospectively or prospectively are: rate of somatic mutations (mutational load), level of somatic copy number alterations (SCNAs) and microsatellite instability. Tumors with high rates of somatic mutations (i.e., sun-exposed cutaneous melanoma, NSCLC, bladder cancer, and microsatellite-unstable colorectal carcinomas) or high SCNA level have a higher chance of benefiting from immune checkpoint blockade than tumors with lower rates of somatic mutations. In order to assess these techniques, we need tumor sample. Furthermore, one interesting field is the better understanding of the impact of immunotherapy on tumor microenvironment, as well as the mechanism of resistance on these new therapies, underlying the necessity of consecutive biopsies during therapy and at progression.

Thanks to the technological advances, in the near future only small biopsy samples will be required in order to proceed with the tests above; therefore, the probability of complications will be minimized.

Another important role of the biopsy is to help oncologists confirm immune-related toxicity. Currently, European Society of Medical Oncology (ESMO) recommends tissue biopsy (skin, liver, gastrointestinal, kidney or lung) if there is clinical or radiological doubt particularly when toxicity is severe (grade 3 or 4). For example, the differential diagnosis of acute elevated aminotransferases during treatment includes drug-induced liver injury (DILI), idiopathic autoimmune hepatitis (AIH), acute viral hepatitis and acute alcoholic liver disease. Liver biopsy can lead to a

revised diagnosis of liver injury etiology and proper therapy [46].

Local administration of the promising new immunotherapy drugs as well as combination of local treatment and immunotherapy emphasize the important role that IRs play and will continue to play in the field of cancer and will continue to play, as these techniques will expand.

Conclusions

In light of the success of immune checkpoint inhibitors in solid tumors, cancer immunotherapies, in general, has generated a tremendous interest in further developing and exploring these strategies across the oncology disease spectrum. Several approaches exist and more than 1500 clinical trials are ongoing.

It currently becomes more and more evident that interventional radiology will have a key role in this development, as there is a growing need for tumor samples as well as local administration of immunotherapeutic drugs.

Despite the efforts undertaken so far, the identification of biomarkers that can predict response on selecting patients for treatment is pending with some exceptions. Sequencing and bioinformatics advances may help to identify new tools in the fight against cancer.

Compliance with Ethical Standards

Conflict of interest G. Coukos reports grants from Bristol-Myers-Squibb, Roche, the National Institutes of Health, Celgene and Boehringer–Ingelheim; personal fees from Roche and Genentech; and support for clinical trials from Bristol-Myers-Squibb, Merck and Roche. A. Denys is a contracted consultant for BTG, Farnham, UK. Patent WO 2012/073188 A1 was issued and licensed to BTG by A. Denys. K. Homicsko reports grant from Roche and is a consultant/advisory board member for BMS, Merck Serono, Roche and AMGEN. L.E. Kandalaft reports that she is a consultant/advisory board member of Geneos. A. Digklia and A. Hocquelet have nothing to disclose. R. Duran reports grant from BTG.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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