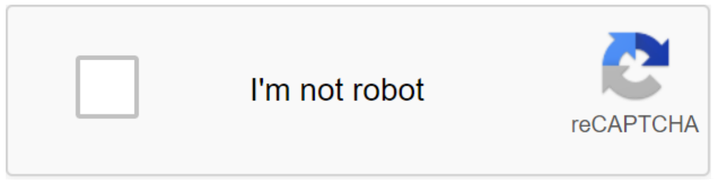

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Adoptive immunotherapy for cancer harnessing the t cell response pdf

Cancer immunotherapy involves using the immune system mechanism to recognize, target and destroy cancer cells. The idea of using the immune system against cancer is based, in particular, on the following properties of its components; immune cells (I) provide constant observation, as they constantly travel throughout the body; II) specifically stimulated against tumors, which are by definition antigenic and often immunogenic; and (III) protect against tumor recurrence, due to induction of specific and long-term memory. However, tumors elude immunosurgery through a well-described procedure such as cancer immunodeficiency. Koebel and colleagues elegantly showed that immunodeficiency involves three major successive events: elimination, balance, escape, and ultimately leads to cancer growth (1). Immunotherapy for cancer appeared at an age, especially after 2000. New knowledge about anticancer immune response mechanisms, new technology platforms for the production of active anticancer compounds and innovative advances in quantifying clinical responses have led to improvements in cancer immunotherapy protocols for the treatment of patients in clinical settings. Since Kohli's first antitumor intervention in 1893, key landmarks include the 1973 discovery of dendritic cells (DCs) (2); development of the first chimeric antigen receptors (CARs) (3) in 1989; cloning of the first tumor antigen in 1991; and the 1995 definition of the first checkpoint molecule, namely the cytotoxic T-lymphocyte associated with protein 4 (CTLA-4) (4). Licensing of clinical trials in 2000 and the first results reported at the time did not contribute to the enthusiasm of most cancer immunologists and oncologists. However, recent evidence strongly suggests a measurable improvement in patient outcomes and, in some cases, effective and long-term responses. In the following sections, we will briefly look at the most popular anticancer immunotherapy protocols and offer possible means of using their synergies for the benefit of cancer patients. The classification of cancer immunotherapy strategies is briefly divided into two main types of interventions: passive and active (Figure 1). The classification is based on the mechanism of action of the used therapeutic remedy, as well as on the state of the patient's immune system. In general, passive immunotherapeutics are used in cancer patients with weak, unresponsive or low responsiveness of the immune system. Passive protocols consist of former vivo-activated cells or molecules that were once inside the body, compensate for missing or insufficient immune functions. Among other things, this category includes tumor antibodies, systemic introduction of recombinant cytokines and the receiving transmission of immune cells pre-activated in the lyse in vivo. On the other hand, active immunotherapy strategies are aimed at stimulating the functions of the effector in vivo. In order to apply active immunotherapy, the patient's immune system must be able to respond to the challenge, competently stimulate and fringe the function of the effector. The most important active protocols include vaccination strategies with tumor peptides or allogeneic whole cells, the use of autologous DCs as vehicles for the delivery of tumor antigens, and the infusion of antibodies aimed at critical T cell activation checkpoints. Finally, although initially seen as a passive intervention, systemic immune responses caused by oncolytic viruses have passed this novel of therapeutic modality to a group of active immunotherapy cancers. Figure 1 Cancer Immunotherapy Approaches are classified as passive and active. Passive immunotherapy involves the use of tumor mabs, cytokines and transmission of receptor cells, while active immunotherapy refers to peptide, DC or allogeneic cell vaccines, checkpoint inhibitors and oncolytic viruses. DC, dendritic cell. Passive cancer immunotherapy Tumor monoclonal antibodies (mAbs) target cancer-specific or cancer-related antigens and cancer-related lys cells using a variety of mechanisms historically, mAbs have been described as magic bullets. The first anticancer murinal mabs were recognized as foreign immune systems of the patient, and the generation of human anti-neck antibodies (HAMA) deprived them of biological effectiveness. Advances in antibody engineering have led to a significant reduction in HAMA responses and currently used mAbs are chimeric, humanized or fully human. The most commonly used mAbs in cancer immunotherapy have a IgG class due to their long-term fitness and serum stability. Naked antitumor mAbs envelop their function by direct induction of programmed cell death when associated with tumor targets and antibody-dependent cellular cytotoxicity (ADCC), dependent on cytotoxicity supplement (CDC) and/or antibody-dependent cell phagocytosis (ADCP). Briefly, mAbs contribute to the ADCC or ADCP-mediated tumor burden gap, through the interactions of their constant fragment (Fc) with fc-receptors (Fc-RIIA and Fc-RIIa on NK cells and macrophagues, respectively) (5). For example, the chimeric mAb rituximab targets CD20 on malignant B lymphocytes that facilitate the recognition by immune effectors, induction of apoptosis by nk cells through the release of perforin/granzimus and fas/faslite interactions and/or phagocytosis macrophages (6). In the CDC, activation of supplementation factors (C) (e.g. C1q, C3b) leads to the formation of membrane attacking complexes, as well as to the set of immune cells and C5a) (7). For example, it has been reported that humanized anti-CD52 mAb alemtuzumab exerts its antitumor activity exclusively by CDC mediation in patients with chronic lymphocytic leukemia leukemia The importance of both ADCC and CDC in cancer immunotherapy is obviously confirmed by the correlation of clinical responses to mab therapy with polymorphisms in the Genes Of Fc'R and C1qA (6). In addition, ADCP facilitates the cross-representation of tumor peptides derived from absorbed apoptotic cells on the main molecules of the histocompatibility complex (MHC), as well as the expansion of tumor CD8 and CD4 T cells, which, among other things, are the main B cells for the production of anticancer antibodies (Abs) (9). Antibodies or antibody fragments can be conjuged through their Fc to radioisotopes (e.g. anti-CD20 mAb 131I-tositumomab), cytokines (e.g. anti-GD2/interleukin (IL)-2 protein synthesis EMD 273063 and toxins (e.g. gemtuzumab ozogamycin, a fusion of cytotoxic antibiotic with a mab aimed at CD33 on leukemia myeloblasts (100). given systemically, in a powerful cytotoxic agent (e.g., the merging of Fc into lactamazo, which converts C-Mel into melphalan) (11). With a certain antigen on the surface of cancer cells, blocking specific downstream signaling pathways and arresting cell proliferation (table 1). Indicative examples include cetuximab and panitumumab targeting epidermal growth factor receptor (EGFR). Both mAbs prevent the binding activation of EGF ligand and the dimerization of EGF receptors and the dimerization of receptors further blocking the PI3K/AKT and Ras/MAPK alarm (12.13). They are used, until now, as a second and third line treatment for metastatic colorectal cancer (CRC). Trastuzumab and Pertusumab are aimed at the truncated form of EGFR, HER2. They suppress the dimerization of receptors, increase its endocytic destruction, tap ACCC and cause apoptosis (14). Other mAbs that target immunosuppressive tumor microocnonics have also shown positive results in clinical settings. Bevacizumab prevents the binding of the vascular endothelial growth factor (VEGF) with its receptors and suppresses angiogenesis. Its use is approved for some solid tumors (e.g. CRC), in combination with chemotherapy (15). Daclizumab, CD25-specific mAb, effectively depletes CD4 -CD25 FoxP3 regulatory T-cells (Tregs) and is approved for the treatment of patients with metastatic breast cancer (16). Finally, bispecific mAbs have also shown promise by acting by overcoming immune effects to cancer cells and promoting the eradication of tumor cells. A new class of such mAbs, artificially produced by bisspecific T-cells (BiTEs), can cause T cells mediated elimination in the absence of T-cell receptors (TCR)-MHC interactions. Blinatumomab is currently the only Food and Drug Administration (FDA) approved by BiTE to treat fireproof or relapsed Philadelphia B-acute lymphocytic leukemia (17). Table 1 Monoclonal Antibodies and Conjugation Approved for Cancer Treatment in Humans (February 2016) The Complete Table of Cytokin Administration demonstrates some efficacy, mainly in combinatorial anti-asxic treatments Although, being one of the first therapeutic interventions in cancer, the use of cytokines as monotherapy is no longer popular. The most well-known cytokines are interferon-alpha (IFN-z), Il-2 and Il-12. The high dose of IL-2, as well as IVN-W, received FDA approval for the use of metastatic melanoma (in 1992 and 2011, respectively) and kidney cell carcinomas (RCC; in 1998 and 2009, respectively), as both act pleiotropically and reportedly have immunomodulating effects on immune cells (18.19). IFN-Z further demonstrated a noticeable suppression on Tregs in tumor microocononation. In particular, the postoperative administration of IVN-W in patients of the RCC for 4 weeks led to a decrease in the frequency of tumor and peripheral blood Tregs (20). Recent in vitro data indicate that the integration of VN-W into the DC protocol has significantly improved its therapeutic effectiveness (21). IL-2 is preferably administered in conjunction with standard treatments such as chemotherapy, other cytokines, peptide vaccines and mabs. For example, the combined administration of IL-2 and IVN-W in IBD patients with metastases in the lungs demonstrated a significant survival advantage (22). In patients with progressive melanoma, the introduction of the gp100 peptide vaccine with IL-2 led to higher rates of clinical response, long-term progression-free and overall survival (OS), compared to a high dose of IL-2 monotherapy (23). Another widely used cytokin is IL-12, which is usually excreted from antigenic cells (APCs) in response to antigen stimulation. Among other biological activities, IL-12 promotes the polarization of CD4 T cells in Th1 cells, organizes antitumor reactions and inhibits tumor Tregs (24.25). Although the first Phase II trial failed due to severe toxicity (26), IL-12 treatment of cococenous T-cell lymphoma (27), non-Hodgkin B-cell lymphoma (28) and AIDS sarcoma Kaposi (29) showed encouraging results. In addition, IL-12 gene therapy with plasmid transfers in electroporation (30) and immunocytokin (e.g. NHS-IL-12) (31) has been tested. Admissions strategies for cell transmission (ACT) significantly improve patient outcomes in solid and hematological malignancies In ACT protocols patients are treated with advanced autologous cells ex vivo, including tumor lymphocytes (TIL), cytokin-induced killer (CIK) or cascading (CAPRI) cells (table 2). TILs are isolated by dissociating tumor samples into single cells and lymphocyte enlargement in vitro in the presence of a high dose of IL-2. Promising results were shown in patients with metastatic melanoma, where the treatment of TIL was very very inducing long-term responses, regardless of previous treatments (32). It is noteworthy that the tumor-reactive infusion cd4' TIL in a patient with widespread metastatic cholangiocarcinoma led to regression of metastases in the liver and lungs (33). CIK cells consist of a heterogeneous population, consisting mainly of CD3-CD56 cells. They are generated by stimulation in vitro mono-nuclear peripheral blood cells with anti-CD3, IL-1 and IVN-W, while the addition of IL-2 and IL-15 further increases their effector function (34). CIK cells are not limited, migrate to tumors and exert their cytotoxicity through the interaction of NKG2D receptors, allowing their clinical application in a wide range of solid and hematological malignancies (35.36). CAPRI cell therapy uses the patient's own peripheral blood monocytes, which represent cancer peptides, to prime in vitro naive T cells in cytotoxic effectors. The CAPRI quartet contains monocytes, DCs, CD4 and CD8 T cells. The procedure followed for their generation begins with autologous stimulation of T cells with OKT3 and IL-2, which then activate monocytes to display more cancer immunogenic peptides. The subsequent co-culture of these monocytes with indelib T-cells premieres the expansion of CAPRI cells, which when infusion, the exhibit increased cytotoxia against tumors. The first results of CAPRI cell therapy in patients with metastatic breast cancer led to an extension of their survival, compared to untreated patients (37), while favorable results were also shown in non-small cell lung cancer (NSCLC) patients. It should be noted that the drug lymphodeling chemotherapy or whole-body exposure usually makes the recipient prone to all of the aforementioned ACT approaches, increasing the reception of the transferred cellular persistence and their antitumulant effectiveness in vivo (38.39). T cells are another variant of cancer immunotherapy, as they can be genetically modified to express TCRs with high greed for specific tumor antigens (table 2). Variable-origin TCR genes (e.g. human or from humanized mice) are cloned into viral vectors and used for autologous T cells transductions in patients. The first clinical trials in patients with melanoma were promising (40). Table 2 The pros and cons of some adoptive cellular approaches to the CARs table, originally built in 1989, are surface proteins that combine a single chain of variable fragments (scFv) antibody recognition of tumor antigen with intracellular T-cell signaling domains (3). The first-generation CAO consisted of scFv, by CD3ζ (41) (table 3). Second- and third-generation CAOs contained additional costhymulal domains, like CD28 and/or CD137, which improved the production of cytokines and the vivo-resistant CAR-modified T cells, respectively. Newly developed T cells are redirected to universal universal (TRUCKs/fourth generation CARs) are modified with the invulnerable vector Il-12 and, with the participation of the sonata antigen, produce Il-12 (42.43). IL-12 sensitizes APCs in tumor microocnononization and produces a local inflammatory response, improving tumor eradication (44). To bypass the modification of T cells for various tumor antigens, universal CAOs with unlimited adaptability to antigen were also developed. These avidin (45) and anti-fluorescein isothiocyanate (FITC) (46) -bearing CARs associate with high affinity any biotinilized or FITC-designated tumor antigen-specific mAb and exhibit powerful anti-tumor activity. Table 3 Characteristics of the first-fourth-generation CAR-engineered T-cells Full Table of First Generation CARs used in early clinical trials have shown no objective clinical reactions. However, clinical trials of hematological malignancies using second- or third-generation CAO have shown noticeable reactions (47). CAR T-meso in patients with mesotelino-express tumors and CAR T cells secreting IL-12 for recurrent ovarian cancer are among the most promising designs (48). Lymphodeling to CAR infusion (38.39), cytokine supplementation, integration of several sosymuleric intracellular domains (49) and expression of chemokin and their receptors (50) increased the durability and homing of CAR T cells to the tumor site, and were strongly correlated with the outcome of treatment (51). However, CAR THERAPY is accompanied by adverse events (e.g. toxicity due to a cytokine storm), which requires the need to regulate uncontrolled or hyperactivity. For this reason, negative approaches to regulation have been developed, such as the inclusion of suicide switches (e.g. the unappuped caspase-9 gene) in CAR T cells. Unfortunately, such strategies have led to the complete eradication of engineered cells from patient circulation (52). In contrast, positive regulatory strategies recently applied, integrated into THE CAR, build a domain that requires both an exogenous signal provided by the user (e.g. rapamycin analogues) and a targeted scFv antigen to activate it (53.54). The clinical effectiveness of such transient CAR-modified T cells should be evaluated. Active cancer immunotherapy Peptide vaccines can generate effective antitumer T-cell responses to an anticancer vaccine designed to induce

tumor-specific or tumor-specific immune reactions in vivo; the most popular category are peptide vaccines, usually consisting of immunogenic epitopes made of tumor or tumor antigens (TSAs or TAAs, respectively). Most tumor antigens stem from products of mutated oncogenes (e.g. K-RAS, BCR/ABL) or tumor suppressor genes (e.g. tumor suppressor) oncogenic viruses (e.g. HPV, HVV, EBV), oncophetic proteins (e.g. CEA, a-FP), cell differentiation proteins (e.g. PSA, Melan-A/Mart-1), reexpressive or abnormal abnormal or modified glycolipids and glycoproteins (e.g. MUC-1, CA-125, GM2). TAAs also include cancer test antigens (CT), the normal expression of which is limited to male germ cells in the testicle (55). In fact, the first tumor antigens cloned were melanoma-related antigen 1 (MAGE-1) and New York's esophagus squamous cell carcinoma (NY-ESO-1), both classified as CT antigens (56). Initial clinical trials of peptide vaccines derived from tsa- or TAA, used as monotherapy, have shown limited efficacy due to a narrow range of immune responses induced in vivo and MHC restriction (57). Single and multiple peptide vaccines limited to individual patients express appropriate MHC alleles, accompanied by vaccines consisting of cytotoxic T-lymphocytes (CTL) and T (Th) cell epitopes, although effectiveness has not been significantly improved. The new generation of antitumor peptide vaccines consists of multi-peptide cocktails, synthetic long or hybrid peptides that include both CTL and Th-cell epitopes. They are administered in combination with other treatments and are used to treat various cancers (e.g. colorectal, lung, pancreas, stomach, prostate and breast). In particular, in breast cancer, vaccines containing her2/neu, MUC1 and CEA epitopes were tested in Phase I-III clinical trials, showing promising results (58). Personalized peptide vaccination (PPV) is also gaining momentum, based on the concept of increasing the already existing immunity of the host. In the last randomized Phase II clinical trial, PPV combined with metronomic low-dose cyclophosphomide in patients with metastatic castrate-resistant prostate cancer long-term OS of those patients who responded immunologically after vaccination, i.e. established peptide-specific humoral and CTL responses (59). Dendritic cells (DCs) are ideal means for delivering anti-cancer vaccine DCs have been described as an adjuvant of nature due to their high potency to initiate and support immune responses (60). Given their potential to stimulate adaptive and congenital antitumor immunity, DCs have been used in recent years as anticancer vaccine vehicles. Traditionally, two DC-based vaccination approaches have been widely applied, direct targeting antigens to DC in vivo receptors and ex vivo generation antigen-loaded DCs. To improve the effectiveness of the DC-based vaccine and given the growing understanding of DC biology, the research focused on the use of the competence of various DC subscenms, optimizing the maturation of ex vivo DC and manipulating the cosy expression of molecules (61). Most widely used THE DC in the clinic differs from the peripheral blood monocytes ex vivo, which are outraged by recombinant commotion macrophag stimulant factor (GM-CSF) and IL-4 (mDCs). Although clinically beneficial, there are both advantages and disadvantages associated with Use. For example, MDCs are easily manipulated before administration, can be loaded with any tumor antigen and optimally activated with a multitude of adjuvants. However, ex vivo production of MDCs is time-consuming and expensive, and a limited number of them are often available. Thus, an attractive alternative is specifically targeted DCs in vivo, i.e. load them with appropriate tumor antigens and activate them for the production of pro-inflammatory cytokines. Although less control over the quality and magnitude of induced reactions is proposed, a number of new molecules undergo preclinical tests, such as immune stimulant complexes (called ISCOMs) (62). Safety as well as the ability of dc-based vaccines to activate tumor antigen-specific CD4 and CD8 T cells in vivo have been thoroughly tested in Phase I-III trials for more than 10 years. The first and only, at the moment, DC-based anti-cancer vaccine that has received FDA approval is Sipuleucel-T (Provenge, Dendreon Corporation) to treat the metastatic asyptomastic hormone fire-resistant prostate cancer. To do this, autologous monocytes are collected from the patient, pulsed ex vivo with the synthesis of the protein phosphate prostatic acid and GM-CSF, and then poured back into the patient (63). In addition, Phase II/III clinical trials using similar approaches in patients with melanoma, glioma and glioblastoma, ovarian cancer, RCC and multiple myeloma induced reliable reactions and improved clinical outcome (64). A relatively new and promising approach involves merging patient DCs with autologous tumor cells, based on the concept that DC/tumor hybrids can deliver, process, and then present a full range of specific TAA patients, including those that are still unidentified. In preclinical models, DC/tumor vaccines have led to the eradication of established tumors. In clinical trials, DC/tumor hybrids were well tolerated, but limited reactions were observed in patients with late tumors. The current operation means to make each hybrid component more immunogenic before merging, for example by pre-activating DC with TLR agonists and pre-treatment of ethanol cancer cells in order to express abundant hazard signals, is expected to improve their therapeutic potential (65). From the autologous to the allogeneic cell vaccine, Autologous tumor cells are the obvious source of TAA for PPV, as they, by definition, cover all relevant taa candidates. Allogeneic tumor cells are also a good source of TAA, as the test tube is immortalized cell lines: (I) are a limitless source of TAA; (II) to ensure large-scale production of allogeneible and III) provide well-defined batches for use in a wide range of patients, eliminating variability in the vaccine, making it easier to compare clinical outcomes and being cost-effective. Allogeneic cell vaccine vaccines whole tumor cells that are transfected before exposure to produce cytokines or express-stimulating molecules, thus presenting increased immunogenicity. When administered to patients, inactivated tumor cells do not multiply, but express and optimally represent a wide range of TA CT cells, ideally organizing an antitumoco reactive immune response (66). A notable category of whole cellular anti-tumor vaccines are genetically transfued tumor cells GM-CSF, commonly referred to as GVAX. GVAX vaccines have already proven to be active against a wide range of cancers, including prostate, NSCLC, RCC, pancreas and melanoma (67). The secreted gm-CSF cytokin acts locally in a paracritical manner, recruits and activates APCs and promotes the absorption of barn tumor antigens from irradiated cells for cross-representation. The most studied GVAX is prostate GVAX, which includes two GM-CSF gene-transfected irradiated prostate cancer cells, PC3 and LNCaP. Although Phase III clinical trials with prostate GVAX have been discontinued due to increased mortality, GVAX pancreatic is widely tested in Phase III trials, especially in combination with checkpoint inhibitors (68). Checkpoint inhibitors release the brakes of the immune system It is known that cancer cells can be destroyed as a result of cell immunity processes, during which T cells recognize and react to tumor antigens exposed on the surface of the APC. However, the optimal activation of T cells against the target antigen, initiated by the interaction of the MHC tumor peptide molecule with TCR, also called signal 1, should be supplemented by the interaction of bone-stimulate molecules on T-cells (CD28) and APC (B7-1/CD80 and B7-2/CD86), i.e. signal 2 (69). Activated T cells also express CTLA-4, a negative T-cell activation regulator that competes for B7 binding, thus counteracting positive CD28 (70) signals. Another described T-cell co-inhibition pathway includes the programmed cell death protein 1 (PD-1) and its PD-L1/L2 ligands, which lead to reduced proliferation of T cells and cytotoxicity, as well as increased susceptibility of T cells to apoptosis (71). In physiological conditions, the pathway of PD-1/PD-L1/2 prevents excessive activity of the T-cell effector, controls tissue damage during inflammation and prevents the development of autoimmune diseases, contributing to tolerance to self-antogenes (72.73). In cancer, the involvement of either of the two molecules leads to the depletion of T cells and down regulation of the antitumor reaction (74). In other words, tumor cells use PD-1/PD-L interaction as a defense mechanism to close the resulting antitumor immune response. Down-regulation functions of T-cells can be reversed by the help of immune checkpoint molecules/inhibitors that block CTLA-4- and/or PD-1-mediated signalling cascades, hence the preservation and and Activation of T cells in micro-tumor nanonoronia (75). In addition, it was recently reported that inhibiting the path of CTLA-4 leads to the depletion of suppressive Tregs and blocking the path of PD-1 revives the functionality of exhausted T cells (76). Most importantly, the simultaneous blocking of both pathways significantly increases the antitumor reactivity of T cells (77). Although after CTLA-4 and PD-1, A variety of immune checkpoints have been identified and numerous clinical trials have investigated the clinical usefulness of their blockade, to date only three immune checkpoint mAbs have received FDA approval for cancer treatment, a CTLA-4 ipilimumab inhibitor (in 2011), and PD-1 blockers nivolumab and pembrolizumab (both in 2014; Figure 2). Figure 2 Schematic representation of important signals about mediation of T cells, APCs and tumor cell interactions. During the activation phase (left), T cells interact with APCs and receive signal 1 (MHC/tumor epitope-TCR) and signal 2 (B7-CD28). Activated T cells express the inhibitory molecule CTLA-4, which is blocked by an ipilimumab, thus allowing their constant activation. During the effector phase (right), activated T cells migrate to the tumor, where their TCR recognizes tumor epitopes in the context of MHC molecules. Pembrolysumab and nivolumab block the PD-1 checkpoint molecule and, consequently, its interaction with the inhibitory regulator PD-L, expressed by tumor cells. As a result, T cells overcome tumor suppression. APC, the antigen representing the cell; MHC, a large complex of histocompamity; TCR, T-cell receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L, PD-1 ligand. Ipilimumab Ipilimumab (Yervoy, Bristol-Myers Squibb) is a fully human IgG1 mAb, blocked interaction CTLA-4 and B7-1/2. As of February 2016, ipilimumab is approved for the treatment of non-resectabian or metastatic melanoma, where it has demonstrated a significant survival advantage (78.79). Currently, 120 open clinical trials are or will recruit patients with various types of cancer who will receive ipilimumab as monotherapy (e.g. for recurrent ovarian cancers sensitive to platinum; NCT01611558) or as a combinatory treatment (e.g. chemoradia for locally advanced cervical cancer; NCT01711515). Pembrolizumab Pembrolizumab (Keytruda, Merck) is a humanized IgG4 mAb that targets PD-1, thereby disrupting its inhibitory interaction with PD-L1/2. As of February 2016, pembrolysumab is approved for the treatment of progressive melanoma that progresses on ipilimumab, and the braF mutant melanoma has progressed to BRAF inhibitor (e.g. dabrafenib, vemurafenib). It is also approved for the treatment of metastatic PD-L1, after progression on platinum-containing chemotherapy and/or on EGFR/ALK-targeted medications (e.g. erlotinibe, hefitinib, cerytinib) for tumors carrying EGFR or or mutation (80-82). Nivolumab Nivolumab (Opdivo, Bristol-Myers Squibb) is a fully human IgG4 anti-PD-1 mAb with the same mode of action as pembrolysumab, but with a 10-fold decrease in affinity to PD-1 compared to pembrolizumab. As of February 2016, it is approved for the treatment of metastatic melanoma progressed on ipilimumab and BRAF-mutated melanoma has progressed to a BRAF inhibitor (e.g. vemurafenib) (79.83). It has also recently been approved for the treatment of patients with metastatic squamous NSCLC with progressive disease on or after platinum-based chemotherapy (84). Nivolumab demonstrated promising antitumor activity in kidney cancer, showing survival advantage and long-term reactions regardless of the level of expression of the tumor PD-L1 (85.86). Most importantly, nivolumab displayed fewer side effects and lower toxicity, compared to ipilimumab (87). Due to the high clinical effectiveness of immune control current inhibitors, the evaluation of their combinatorical synergeutic oncology effects is actively studied in clinical trials. In the first phase, I evaluated the combination of ipilimumab plus nivolumab in patients with advanced stage III/IV melanoma. Patients who progress on ipilimumab have achieved positive antitumor reactions after subsequent nivolumab treatment, suggesting that consistent administration of immune checkpoint inhibitors may be used to restore antitumor immunity in patients progressing in treatment with a single inhibitor (88). Among other things, Phase III trials (NCT018444505) assessing the same combination are currently ongoing for patients with previously untreated irrefutable or metastatic melanoma. In general, the licensing of immune control card inhibitors has produced impressive therapeutic results, thus opening new boundaries for their use in other types of cancer, including brain tumors, squamous cell carcinoma of the head and neck, adenocarcinoma of the pancreas, bladder tumors, stomach and breast cancer. Oncolytic viruses directly mark tumors and systemically stimulate the anti-tumor immune responses of lytic viruses, by definition, multiply inside the host cell, which subsequently collapses. Oncolytic viruses are harmless viral strains that target and kill tumor cells, but are reportedly also shown to cause immunity mediated by tumors. In particular, the replication of the virus in cancer cells, followed by the lyses of cancer cells, leads to the release of more viruses, as well as tumor antigens (89). Consequently, the absorption of the APC antigen indirectly contributes to the systemic immune response of T cells (90.91). Genetic engineering viruses can further enhance their oncolytic properties and redirect them exclusively in close proximity to the tumor (92). The most famous oncolytic virus-based therapy, Talimogene laherparepvec (T-VEC), consists of a GM-CSF-transified modified form of herpes simplex virus-1, which infects and only tumor cells, with the simultaneous production of GM-CSF. After an international randomized Phase III study in melanoma patients (OPTiM), where T-VEC exhibited endoprostic treatment responses, this oncolytic virus was the first to gain FDA approval for use in patients with melanoma with non-resistant tumor lesions (93). Oncolytic viruses have also shown therapeutic potential in preclinical models, in combination with other immunotherapy methods such as ACT (e.g., increased turnover of tumors and cytotoxicity of transducted T cells loaded with vesicular stomatitis virus) (94.95) or control dog inhibitors (e.g., tumor regression after the introduction of strains of vaccines and anti-1la). Some problems need further research, especially if oncolytic viruses are injected systemically. They are associated with increased toxicity, mainly due to sequestration in different organs; ineffective viral spread, due to macrophagus cleaning or neutralization of existing Abs and supplement; and reduced infiltration in tumor micro-ornoronia, due to low extravasation and the presence of connective tissue and extracellular matrix barriers (97). Some new approaches that may further enhance the anticancer immune response New delivery methods facilitate the vivo transmission of therapeutic molecules In recent years, different nanocarrier systems have been evaluated, as they make up an attractive tool for high-target therapy. Nanomaterials can reach selective, localized and even simultaneous delivery of multiple immunomodulators, TAA and drugs to target tumor sites or lymphoid tissue (98). Among the most commonly used nanoparticles are polymer nanocariers such as FDA-approved synthetic biodegradable polylacide, lipid nanocarers such as liposomes and phospholipid micelles, acid-degrading hydrogels, gelatin-based nanocariers and state-of-the-art metal nanocarers such as quantum dots. For example, gold nanoparticles have been shown to increase the immunostimulatory effect of CpG oligonucleotide in combination (99). Other preclinical studies have reported that poly-milk-coglic acid nanoparticles deliver melanoma antigens induced by effective antitumor reaction CTL (100). In general, nanocariers bypass the problem of inconsistent delivery and absorption of antigens and represent a promising anti-orangutan way for the future. The use of immunogenic cell death in anti-tumor immunity The new concept, first described in 2013, is that some cancer treatments, such as radiation therapy and chemotherapy using specific (e.g., atracycline, oxaliplatin), cause so-called immunogenic cell death (ICD) in tumor cells. ICD is a cell death mode characterized by: (I) excessive and enlarged lyses and the release of tumor cell components, including intracellular intracellular cells Signals II) increased activation of DC; (III) high absorption and presentation of tumor antigens DCs; (IV) cross-primer and ctL extension specific to tumors; and (V) the production of tumor mabs. Chemotherapy can also alter the frequency and function of regulatory immune cells, including Tregs, myeloid suppressor cells and tumor-related macrophages. Important intermediaries that act as hazard signals and, in practice, as vaccines are on the ground and are released during ICD, are highly-moving group box 1, calreticulin, ATP and polynucleotide fragments (101). At present, we have yet to understand the molecular and cellular mechanisms underlying ICD. This may eventually lead to the development (I) of algorithms for optimal management of cancer patients, based on ICD induction with this anti-cancer treatment; and (II) combinatory immunomodulation treatment with ICD-inducing chemotherapy/radiotherapy. In the case of the latter, promising clinical trials of various types of cancer (e.g. cervical, head and neck, progressive and metastatic melanoma) have already been achieved, assessing the combination of local radiation exposure with ipilimumab (102). Future Prospects Over the past decade we have experienced significant progress in the treatment of cancer. A better understanding of the cellular and molecular pathways leading to tumor development, escape and spread has been clinically translated into new treatment options. There are new classes of molecularly targeted drugs, which quickly received approval for use in the human body. We were able to reprogram our own components of the host's immune system to target and attack cancer. We have extended the survival of patients who previously did not have effective treatment options. We have improved the quality of life of cancer patients and survivors. Most importantly, we noted that immunotherapy interventions control tumor growth/recurrence for many years after treatment is completed. Thus, it is not surprising that in 2015 16 new drug approvals and 7 extended SOBR readings related to targeted or combin therapy. What we have also learned is that the combination of different immunotherapy should be elegantly organized on the one hand to enhance anticancer reactions (PUSH) and on the other hand, neutralize or eliminate negative immune regulators (PULL) (Figure 3). Figure 3 Push and PULL approach can optimize anticancer immunity. Appropriate selection of tumor antigens stimulates antitumor-reactive immune responses, which can be further enhanced by multiple approaches (e.g., sestus stimulate molecules; CLICK). A robust cancer response may subsequently be amplified and maintained by blocking regulators (e.g. CTLA-4; PULL), which leads to highly effective cancer immunotherapy. We're on our way to treating cancer. In the future, we need to focus on more specific issues, such as development Personalized treatment (e.g. PPV), improved managed drug delivery (e.g. with nanoparticles), the use of synergy between different cancer treatments (e.g. chemotherapy and control dog inhibitors) and the expansion of the target repertoire of drugs by discovering new targets, new drugs, and new molecules targeting multiple molecular pathways (e.g. panthyrosine). But we also need to invest in the discovery of predictive/predictive cancer biomarkers that can fairly early and reliably guide treatment solutions. Some biomarkers are already available (e.g. PSA, CEA, BRAF V600E mutations), while others are widely studied (e.g. CPC, MIRNA). Thus, cancer patients who can benefit from immunotherapy interventions will be selected early, properly treated and hopefully cured. Funding Recognitions: The study was supported by the European Union FP7 Potentials Grant REGPOT-CT-2011-284460, INsPiRE (to OT) and IKY Scholarships of Excellence for Postgraduate Excellence in Greece-Siemens (for PS). Conflicts of interest: Authors have no conflict of interest to declare. References Koebel CM, Vermi W, Swann JB, et al. Adaptive Immunity supports occult cancer in an equilibrium state. Nature 2007;450:903-7. (Crossref) (PubMed) Steinman RM, Con SA. Identification of a new type of cell in the peripheral lymphoid organs of mice. I. Morphology, quantiation, tissue distribution. J Exp Med 1973;137:1142-62. (Crossref) (PubMed) Gross G, Waks T, Eshhar Z. Expression of immunoglobulin T-cell receptors are chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci U S A 1989;86:10024-8. (Crossref) (PubMed) Leach DR, Krummel MF, Allison JP. Increase of antitumor immunity by blockade of CTLA-4. Science 1996;271:1734-6. 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