Regulatory Landscapes in Approval of Cancer Vaccines

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Abstract

Cancer vaccines are hypothesized to trigger an immunological reaction against cancerous tissues. The scope of expanded clinical activities in the cancer vaccine research programmes can be acknowledged by the fact that around 2000 trials are registered under clinical cancer vaccines programme. The research activities in the cancer vaccine research area have gained a boost following the marketing authorization of Sipuleucel-T—the very first cancer vaccine in the US and EU. Though the regulatory guidelines for already existing cancer therapies like chemotherapy, radiotherapy are well established. Recently, the guidelines regarding regulatory aspects for cancer vaccines are developed. However, these guidelines are advisory in nature about the clinical requirements. However, the cancer vaccine development is relatively new area of research. There exists a huge scope for innovative strategies in this field. Hence, bilateral talks with the regulatory body are mandatory requirement to discuss and deliberate the clinical development plan on case-by-case basis. Thereby, the specific issues related to the quality of product under development are taken into consideration. All such regulatory aspects pertaining to the development and approval of cancer vaccines are discussed hereby in this chapter.

Keywords

T-cells · Antigens · Cancer vaccines · Immune system

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17.1 Introduction

Cancer is amongst the most serious health concerns among all age groups around the globe. Current available treatment approaches for cancer have serious toxicity concerns. Hence, a relatively non-toxic approach that neutralizes cancerous growth by the immune system of the patients is a recent subject of interest for researchers. The domain of research and innovation in this area expands with high profile success owing to the advances in research methodologies and diagnostic techniques. However, to overcome regulatory hurdles, it is essential to demonstrate proof of concept and evidence supporting safety and efficacy. Furthermore, it must clarify the proposed mechanism of action. Hence, the clinical development plan must be constructed keeping the same in mind. However, to demonstrate mechanism of action in non-clinical program, a different approach should be considered. One must bear vast knowledge regarding regulatory guidelines regarding clinical development plan and clear plan for its justification and ensured regulatory input.

In some instances, the immune system has exhibited the ability to demonstrate the immune response against tumor. A successful, specific, and effective immune response would be the one which destroys not only the tumor tissue specifically but also toxicity to normal tissues and risk of second malignancy. Long-lasting immune memory and the specificity of cancer vaccine would induce destruction of existing tumor (therapeutic benefits) or identification of antigens on premalignant cells by immune system (prophylactic benefits).

The approaches in cancer immunotherapy include passive immunization (monoclonal antibodies (MABs) specific to tumor cell antigen), utilization of tumor specific cells (e.g., lymphocytes that penetrate melanoma tumor), silencing of immune check points to enhance immune response (anti-PD-1 and CLTA4), and CAR (chimeric antigen receptor) T cell engager technology (Heelan 2014). Recent findings in tumor pathophysiology and associated immunity have opened a broad gateway of better understanding of balance among immune cell activation, tumor cell proliferation, and escape mechanisms. This information can be utilized to assert the need for safe, effective, and successful cancer vaccines. Existing regulatory guidelines regarding antineoplastic medicinal products in the EU (European Union) and US (United States) mostly consider MABs and cytotoxic treatment approach. However, later on guidelines pertaining to cancer vaccine have been included. As different approaches are undertaken for different types of tumors, it becomes very cumbersome for both the drug developers and the regulatory personnel to ensure adequate quality, clinical and non-clinical attributes.

17.2 Overview of Cancer Vaccines and its Types

17.2.1 Cellular-Based Strategies

Preclinical studies indicate that CD8+ T cells specific to tumor play a significant therapeutic role. On this preclinical observation, majority of the cancer vaccines attempt to stimulate these cells. The most widely utilized immunization techniques for activating CD8+ T lymphocytes have relied on major histocompatibility complex (MHC) class I restricted peptide epitopes on tumor associated antigens (TAAs). They enhance presentation by endogenous antigen presenting cells (APCs) after administration with several adjuvant preparations (containing cytokines and toll-like receptors ligands). In order to evaluate protein amino acid sequences for candidate MHC class I members, peptide vaccines use computer-based algorithms. These candidature epitopes are evaluated in vitro for their ability to bind with human leucocyte antigen molecules, to be processed and presented naturally by cancer cells, as well as immunogenicity (able to stimulate CD8+ cells). Most of these epitopes have also been evaluated in mice models (to either extremely comparable human antigens, mouse self-antigen homologs, transgenic, or transfected models) and prove to possess tumor rejection antigen therapeutic characteristics. Another frequent strategy for stimulating CD8+ T cells specific to TAA is to prepare TAA-based vaccine containing autologous APCs like dendritic cells. This method considers the fact that tumors might impart a deleterious impact on endogenous APCs (Kiertscher et al. 2000). Tailored APCs can successfully stimulate antitumor T cells. However, these tailored APCs must be free of tumor-derived substances but should possess appropriate growth factor and immunological signals.

Another technique employs tumor cells (a complicated and incompletely defined antigens array, mutant antigens specific to tumor), which are frequently modified using cytokines like granulocyte-macrophage colony-stimulating factor (GM-CSF) or manufactured using adjuvants (or both). The whole set of mutations specific to tumor as well as all the MHC molecules are present on these cells. Another technique makes use of viruses' inherent effective infectivity to infect tumor antigens encoded cells. Oncolytic viruses are also used in viral strategies. It comprises autologous antigen-presenting cells that have already been loaded with GM-CSF and TAA prostatic acid phosphatase. It received approval for prostate cancer (metastatic) based on evidence from phase III clinical studies that showed the increased survival rate by around 4 months (Kawalec et al. 2012).

17.2.2 Peptide-Based Strategies

The most prevalent ways of cancer vaccination are to give epitopes of MHC class I restricted peptide produced from common TAAs to stimulate rare particular CD8+ T cell clones which respond to self-antigens (Kissick et al. 2014). Preclinical studies show the possibility of such vaccinations having a significant clinical utility (Komita et al. 2008; Zhao et al. 2012). Peptides crafted in adjuvants even without cytokines

like interferon γ and TLR agonists or GM-CSF have demonstrated therapeutic benefit in clinical trials (Slingluff et al. 2013; Pollack et al. 2014). Vaccines relied on a peptide or perhaps many peptides can be administered either individually or with Montanide ISA-51 in conjunction with a cytokine to stimulate APCs, additional adjuvants (like a particular TLR ligand to stimulate and mature APCs), or the peptides pulsed on to autologous APCs or a combination of these approaches. TAA-specific cytotoxic T cells were observed to be activated in mice models upon administration of IFA like oil-in-water emulsion of Montanide ISA-51(Fourcade et al. 2008; Kenter et al. 2008; Schwartzentruber et al. 2011). Data revealed that adjuvanticity of Montanide were also altered when olive oil source was used instead of beef source in manufacturing of Montanide (Rosenberg et al. 2010). A current issue related to IFA is that it may cause T cell buildup at immunization sites rather than fostering systemic immunity (Hailemichael et al. 2013). As peptide-based vaccines are tried in preclinical as well as clinical trials, appropriate vaccine formulations and adjuvants are constantly being developed (Bezu et al. 2018). Peptide-based techniques offer economic advantages in terms of cost of production as nine to 10 amino acid peptides are conveniently as well as inexpensively produced. Large-scale production is feasible, also the stability of peptides remains robust upon storage and transportation. Tragically, those who fail to express typical HLA cannot be tackled with this kind of vaccines due to HLA restrictions. Furthermore, CD4+ helper T cells cannot be triggered by the typical MHC class I binding short peptides, limiting the activity of CD8+ cytotoxic T cells. Although no data on the type of the "aid" provided by heterologous helper peptides exists, the insertion of non-tumor specific aid like tetanus, keyhole limpet hemocyanin (KLH), or pan-DR binding synthetic helper (PADRE) peptides has addressed this obstacle.

Another clinically effective method is to use synthetic peptides that are capable to encompass numerous epitopes of MHC class I and II (Welters et al. 2010). These subcutaneously injected long peptides with 23–45 amino acids have demonstrated better efficacy, presumably due to effective processing, and presentation route, ultimately leading to greater T cell activation (Rosalia et al. 2013). The data obtained in phase III clinical trials suggest that complete tumor antigen protein method allows for the absorption, processing, as well as the presentation of several antigen peptides of MHC class II and MHC class I (although with maybe lesser efficiency) (Dreno et al. 2018). Despite being formulated with an improved adjuvant, this vaccine contains full-length protein but still to achieve clinical objectives (Hirschler 2014). Several peptides can be administered simultaneously, targeting multiple antigens and T cell clones at the same time (Slingluff 2011). A study that combines cyclophosphamide (pre-vaccine) with GM-CSF and various peptides discovered that better survival was correlated with antigenic range of response and decreased myeloid-derived suppressor cells (MDSCs) and suppressive circulating regulatory T cells (Tregs) (Walter et al. 2012). Studies on mouse models support the use of multiple-antigen peptide vaccines in combination with chemotherapy (Disis et al. 2013). Peptide vaccines may potentially be effective in preventing pre-malignant lesions from advancing to cancer. A mucin 1 TAA peptide-based method was evaluated in a recent clinical study to prevent the development of colon adenoma

to colorectal cancer (Kimura et al. 2013). Nearly half of the 39 individuals tested exhibited high immunogenicity developed by vaccine. Notably, in more than half of the individuals having advanced colonic adenoma, a significant number of immunosuppressive MDSCs were already present. This suggests that circulating MDSCs could serve as a biomarker to access the response to vaccine and that previous vaccination should be investigated, since systemic immunosuppression may even be caused by premalignant lesions.

17.2.3 APC-Based Strategies

A diverse population of APCs comprises dendritic cells which may effectively absorb antigens and subsequently process and present them to CD4+, CD8+ T cells, additionally include immune response modifying signals such as the release of cytokines. Interferon, tumor necrosis factor, and IL-2 mediate a type 1 response, which enhances the stimulation of cytotoxic CD8+ T cells (Palucka et al. 2011; Palucka and Banchereau 2013).

17.2.3.1 Dendritic Cells

Clinical studies of dendritic cell-based vaccines are often one-of-a-kind, including personalized patient immunization procedures and just one clinical trial arm. As a result, comparing trials and drawing clear inferences regarding the efficacy or different methods is challenging. CD34+ progenitor cells and monocytes were examined, and antigens such as complex tumor lysates possessing non-malignant tumor-related antigens, in addition synthetic MHC class I restricted peptides, were employed. Vaccines were administered intravenously, subcutaneously, and intradermally. All these variables might have an impact on the clinical outcomes observed. The dendritic cell-based vaccines were found to be safe practical, and immunogenic, and in certain individuals, they could produce clinically meaningful shrinkage of tumor (Hsu et al. 1996; Banchereau et al. 2001). Numerous significant clinical studies using dendritic cell vaccines have recently been reported. In a study with dendritic cells pulsed with heterologous PADRE peptides and mucin 1-based peptide administered subcutaneously in individuals having renal cell cancer, objective immunologic as well as clinical results were observed (Wierecky et al. 2006). Mucin 1 was a high-ranking antigen in the National Cancer Institute's prioritization study (Cheever et al. 2009). A modest dose of IL-2 was given in conjugation with these dendritic cell vaccines. In another trial, individuals suffering from acute myeloid leukemia were administered vaccines containing WT-1 TAA mRNA loaded dendritic cells. These individuals were under remission following normal therapy. These individuals demonstrated immune stimulation and enhanced clinical response. Another study that looked at dendritic cell-tumor fusions in participants prior to and after the transplantation of autologous stem cell discovered antitumor autoimmune response as well as disease decrease (Rosenblatt et al. 2013). Surprisingly, all of these studies employed a dendritic cell vaccine combination method, in which

systemic cytokine therapy and standard care therapies were combined with vaccines loaded with antigens (Galluzzi et al. 2012).

17.2.4 Tumor-Based Strategies

Early research focused non-development of cancer vaccine discovered that the tumor cells that had been destroyed as well as modified to produce immunostimulatory cytokines such as GM-CSF may be injected into the mice (Dranoff et al. 1993; McBride et al. 1992). Autologous tumor cells-based approach of cancer vaccine preparation was suitable but quite complex. The evidence supporting clinical testing of autologous, syngeneic, or allogeneic tumor cells expressing increased levels of GM-CSF due to transfection justified clinical study with some clinical and immunological responses (Soiffer et al. 1998; Nemunaitis et al. 2004; Luiten et al. 2005).

17.2.4.1 Cell Lines

Allogeneic cell lines had been investigated, either with autologous tumor cells or alone. The G-Vax platform is still being investigated, and it is an element of a "prime boost" combined vaccine research which includes participants having pancreatic cancer. These participants are administered with recombinant Listeria bacteria encoding TAA mesothelin, alone or with a G-Vax consisting of two cell lines of allogeneic pancreatic cancer (Le et al. 2012a, b). Furthermore, numerous injections are achievable without being hampered by induced neutralization by antibody, along with that the addition of bacteria mimics many elements of a genuine infection by activating foreign pathogen pattern recognition receptors or TLRs. Other individualized approaches utilizing autologous tumor antigens involve the use of tumor lysates for loading APCs ex vivo and the fusion of tumor cells with autologous APCs. Many of them are evaluated in initial stage clinical studies, with encouraging results. In rare situations, immune responses to unidentified foreign helper proteins and tumor lysates have been shown (Chakraborty et al. 1998; Geiger et al. 2000).

17.2.4.2 Autologous Tumor Cells

Transfection of APCs with tumor genomic DNA can also be done using autologous tumor cells (Kim and Chopra 2006). This permits unidentified altered tumor related unique gene products to be produced as well as given to the immune system for activation.

17.2.5 Virus-Based Strategies

As previously stated, if the pathogens are introduced in cancer vaccines, they can significantly boost immune response as tumor antigens are presented. Although TLR ligands like polyIC/polyICLC or CpG molecules are used in peptide-based vaccines, pathogens possess complex arrays comprising molecules capable of activating

several immune stimulation channels. Vaccines against Gardasil and human papillomavirus (HPV) Cervarix are approved to prevent cervical cancer caused by the HPV. They function by inducing humoral immunity towards viral capsid proteins that have been organized into viral particles non-infectious in nature. However, they are ineffective against malignancies developed in infected people. Viruses, particularly adenovirus, were employed as vectors for the purpose of active immunization with tumor antigens by injecting into muscle tissue with rapid transfection (Meng et al. 2001; Butterfield et al. 2014), leveraging their intrinsic infectivity. To transduce antigens into APCs, viruses have been utilized earlier (Arthur et al. 1997; Schumacher et al. 2004). These transduced cells exhibited activation or inhibition as a set of consequences due to each virus. Direct delivery of viral vectors can neutralize antibody responses preventing recurrent usage; however, following vaccination using ex vivo transduced viral APCs, the production of neutralizing antibodies is limited. But, clinical utilization of viral vectors can be complicated logistically, including the need for therapeutic grade virus manufacturing. Some of these restrictions can be overcome by using virus-related prime boost using viral backbones of heterologous nature encoding tumor antigens. This strategy has been demonstrated by the fowl pox virus and vaccinia virus prime boost for prostate cancer, expressing the TAA and PSA and the intercellular adhesion molecule 1 (CD54), lymphocyte function-associated antigen 3 (CD58), and costimulatory markers B7–1 (CD80) (Madan et al. 2012). This intriguing technique has enhanced survival in individuals with prostate cancer, and it is still being explored in late-stage clinical studies (Smith and Kantoff 2010; Gulley et al. 2010). This team is also working on viruses that encode mucin 1 and CEA rather than PSA to be used against various types of cancer. Oncolytic viruses drive the trans-activator early genes like E1b as well as E1a, as well as viral amplification from a tumor-specific promoter (which includes promoters driving TAAs such as human telomerase reverse transcriptase (hTERT), PSA, and fetoprotein) (Kanerva et al. 2013). Vaccinia viruses are also employed for this purpose. To increase tumor specificity for viral multiplication and neutralization, one approach has induced viral serpin genes mutations (Guo et al. 2005). Additional customization is being explored, including the use of chemokine-encoding genes or combinations with co-stimulation (John et al. 2012; Li et al. 2012). Herpesviruses have additionally been utilized in cancer vaccination as oncolytic viruses. A possible approach has been to include GM-CSF as an adjuvant or APC growth factor into herpesvirus vectors that proliferate. T-VEC, one of such vectors, had recently been evaluated in melanoma sufferers in a phase III experiment (Kaufman and Bines 2010). The experiment estimated a 26% rate of objective response and an 11% rate of full clinical response in individuals carrying stage IIIB-IV melanoma (Ross et al. 2014). However, it will be critical to explore immune response mechanisms.

17.3 Regulatory Considerations

The regulatory body ensures quality safety and efficacy before granting marketing approval to a medicinal product. This function of regulatory body ensures that the medicinal product has positive benefit to risk ratio in an indicated set of population. Even after marketing approval clinical safety data are continuously collected which helps to ensure that benefit to risk ratio stays positive after marketing approval also. Rare adverse effects undetected in initial clinical experiments on limited number of people can be detected in this way. Like all other products, cancer vaccines also have to comply to the need of regulatory and pharmacovigilance requirements along with proper risk management plan. Here, regulatory requirements mean the requirements for the benefit: risk ratio to remain positive.

The US-FDA (Food and Drug Administration) and EMA (European Medicines Agency) which are regulatory bodies for the United States and Europe, respectively, regularly keep watch on quality, clinical, and non-clinical aspects by releasing guidelines regarding them. ICH guidelines cover regulatory as well as multidisciplinary aspects along with quality safety and efficacy issues. The ICH (International Council for Harmonisation) releases harmonized guidelines in the US, Japan, and European Union; hence, they are very useful for drug developers as they provide guiding principles for multi-regional drug development approach.

17.3.1 Quality Considerations

EMA has issued guidelines for variety of products like gene therapy products, cell therapy products, etc.; but due to continuously growing knowledge of tumor pathophysiology as well as immune system along with novel therapeutic options such as ATMPs (Advanced Therapy Medicinal Product), it becomes unattainable to accommodate all scenarios in any fixed single guideline. Although guidelines have regulatory purpose, they should not be mandatorily followed if not feasible. Sometimes, if a new understanding about the disease emerges and if the drug developers can firmly justify their position based on this new understanding, they should consult the regulatory body regarding the differences between existing guidelines and the findings of drug development program. The drug developers must have a good quality data and sound rationale to support their claims. Quality assessment of cancer vaccines is more complex and challenging. Hence, for some cancer vaccines, case-by-case release specifications must be agreed upon provided that these specifications must be in accordance with the product's mechanism of action.

17.3.2 Non-clinical Considerations

For non-clinical trials, selection of non-clinical model is governed by the target tumor and cancer vaccine type. Various products like proteins, peptides, and cells, e.g., tumor cells, T cells, and dendritic cells are tested. In-vitro manipulated cells,

genetically modified cells, expanded cells, and fused cells were also tested. Vaccines combinations with adjuvants, vectors, cytokines, and immune checkpoint inhibitors have also been tested. However, in some instances, due to unavailability of suitable non-clinical model, demonstration of mechanism of action and proof of concept may be difficult or impossible. This problem arises more prominently during development of autologous personalized vaccines. In this case, while planning the experiments, use of pre-clinical models would vary from case to case.

In some cases, the murine model can demonstrate the proof of concept which extends the base for clinical development; however, in these cases also, differences arise due to differences of patients in comparison to the murine model. Generally, young mice are utilized for the experiments. Therapeutic vaccines are used in patients who might be having tumor for long period of time. Owing to prior radiotherapy or chemotherapy and tumor specific suppression, such patients may have immunosuppression and tolerance to tumor. In case if non-human primates are used, prominent immune system related inter-species differences are observed (ICH n.d.; Sathish et al. 2013). Hence, non-human primates are not recommended.

Human tissues are tested in vitro to check how TAA are distributed and to support the desired outcomes of modifying candidate antigen (Badaracco et al. 1981). Antigen expression can be visualized using tumor cell lines and tumor tissues. Proof of concept can be established by checking cell count and activation status of tumor penetrating cells like CD4+ and CD8+ T cells, MDSCs, dendritic cells, and tumor infiltrating myeloid cells (Horn et al. 2021). Proof of concept can be further supported if it is possible to test the tumor sequentially after vaccination.

A separate section on cancer vaccines is available under anticancer products in EMA guidelines (European Medicines Agency 2012). The EMA guideline states that "Non-clinical in vitro and in vivo proof-of-concept should be presented to justify the planned starting dose and phase 1 studies." However, there is some limitation for instances in which relevant non-clinical model is unavailable. This caveat considers the challenges in planning non-clinical program for few types of cancer vaccines. In such cases, proof of concept can be acceptably established by in vitro experimentations with human cells.

17.3.3 Clinical Considerations

In case of few cancer vaccines, due to limitations in non-clinical study plan, human in vivo studies are undertaken to establish the mechanism of action of cancer vaccine product.

17.3.3.1 Immune Status Pre- and Post-Vaccination

Immune system baseline considerations may differ in animal models from human patients. Prior therapy and older age may be the primary reasons for immune function reduction. The process called immunoediting is the defensive mechanism for tumor to befool the immune system and to evade detection and elimination by the immune system (Dunn et al. 2004). In addition to this, it is observed in early

tumorigenesis that tumor microenvironment also exhibits immunosuppression (Predina et al. 2013).

All these factors affect the individual patient's response to the cancer vaccine. CD4+ cells, CD8+ cells, serum Igs, dendritic cells, MDSCs, and tumor antigen associated specific T cells must be measured during a clinical program as they indicate the baseline immune status. These parameters affect the prognosis as well as individual patient's response to the vaccine. If early phase studies indicate a correlation between baseline status of immune system and patient's response to vaccine, these data can be utilized to design the clinical trial program.

17.3.3.2 Changes Following Vaccination

Periodic in vitro testing gives idea about therapeutic efficacy of vaccine and can be the source of crucial data in early development clinical phase (Pagès et al. 2009). Ex-vivo method of direct peripheral blood analysis can produce more satisfying outcomes as compared to in vitro testing of expanded cells from peripheral blood. Although it remains well-established fact that the changes in immune cells within the tumor cannot be entirely indicated by peripheral blood analysis, this can be a preferred method to assess pharmacodynamic effect in absence of tumor biopsies. Assessment of peripheral blood for tumor antigen associated T cells is very relevant method to establish pharmacodynamic effect. However, additional phenomena like epitope spreading that might be an element of the effect proposed thereby cannot be fully reflected by this method. Establishing the pharmacodynamic effect strengthens the proposed mechanism of action, supports the proof of concept, and helps in determining the dose. This information is very crucial in determining optimum treatment duration.

To establish proof of concept, all the available clinical data are recommended to be utilized as the non-clinical data may not provide sufficient evidence in this regard.

However, major concern about cancer vaccines is the paradox that they can sometimes affect the tumor infiltrating cells and demonstrate enhanced tumor-specific immunosuppression which raises the concern about safety of cancer vaccines (Zhou et al. 2006). Hence, it becomes very crucial to establish proof of concept and pharmacodynamic readout after vaccination. If these types of evidence are available in human, they should be well understood before planning pivotal investigations.

Prophylactic vaccines on the other hand offer lesser obstacles as far as overcoming of immune suppression is concerned. In this case, the subjects under question are not cancer patients; they are rather high-risk individuals with pre-cancerous lesions (Finn 2014). Hence, selection of patients and assigning of suitable endpoints in clinical studies may differ for prophylactic vaccine than for therapeutic vaccine. In such cases, the need for development as well as validation of surrogate end points arises (Gilbert and Hudgens 2008). As the regulatory guidelines are not very well established and very limited knowledge and experience is available in this area, it becomes essential to have two-way communication with regulatory body. This is recommended to be done after acquiring good initial clinical information and a strong basis for future development. In case of therapeutic cancer

vaccines, studies for clinical dose determination with reference to periodic monitoring of immune functions are required. The guidelines also assert the importance of descriptively elaborating the analytical assays performed during the development of cancer vaccine. In cases wherever possible, serial tumor biopsies are performed but the outcomes can provide marker for anticancer action. In such case, the proof of concept can be established from the data generated in early clinical studies wherein few numbers of subjects are subjected to serial tumor biopsies. Although it is not mentioned in guidelines, imaging techniques can also be used to establish evidence for such response in case of tumors for which safe biopsies are not possible.

The patients with large tumors and late-stage disease will show immune suppression and limited life expectancy which makes it difficult to select group of patients for pivotal clinical studies. Hence, EMA guidelines in this regard suggest selecting those having a low or minimum illness burden.

Newly detected cases are not pretreated; immune stimulation approach in such patients may provide greater likelihood of success. Nevertheless, a satisfactory justification for use of such patients must be provided owing to existence of alternative therapies. If a good proof of concept and a sound rationale supports this approach, then it is advised to discuss with regulatory body in order to develop suitable clinical plan. Delayed response for efficacy read-out is allowed for cancer vaccines as per the guidelines which suggest that "revised criteria defining progression is accepted if properly justified." This is with reference to revised RECIST (Response Evaluation Criteria for Solid Tumors) criteria highlighting the possibility of time lag in producing effective immune response hence delayed tumor response in contrast to anticancer agents (Wolchok et al. 2009). EMA recommends overall survival (OS) as the core efficacy endpoint.

While overall survival (OS) is the clear objective, it may be acceptable if the sufficient proof of concept and significantly increased progression-free survival (PFS) is demonstrated by a cancer vaccine in comparison to a suitable comparator. Additional information on post-licensing OS, on the other hand, will be extremely crucial in these scenarios to assure that there is no trace of any significant consequences on OS.

A double-blind trial is employed for evaluating PFS. When double blinding is not practicable, the trials should employ blinded effectiveness assessment. The blinded evaluators should review the radiological examinations if they are the primary measures of effectiveness. The FDA guidance to industry on clinical aspects of therapeutic cancer vaccines (Guidance for industry n.d.) covers a more extensive overview, including the design of companion diagnostics. Yet, as with the EU guidelines, the concerns of the patient group to be investigated as well as determination of realistic endpoint remains unresolved. If the patient group selected has no or little residual illness, the effectiveness objective of illness recurrence will need a longer period of monitoring. The FDA considers immune response monitoring to be experimental, and relevance of such measures is acknowledged as valuable in proof of concept, dosage determination, and probable association with clinical effectiveness. For proof-of-concept purposes, the FDA encourages the utility of exploratory biomarkers as well as offers some recommendations on multi-antigen and adjuvants

treatment. Given the variety of therapeutic vaccination approaches, the guideline suggests that the major clinical outcomes have clinical meaningfulness and reviewed with the FDA.

Following a study of the guidelines of FDA and EMA, it is obvious that the essential standards for safety, efficacy, and quality stays the same as that for other products, and the pathway to marketing authorization would be case-by-case. When available guidelines do not cover the strategy employed in the development of new drug, as is intended for therapeutic as well as all prophylactic cancer vaccines, it is recommended that discussions with regulatory bodies be held to reach consensus on the grounds of a well-justified methodology and well-thought-out program for clinical development.

There are yet no regulatory guidelines for prophylactic cancer vaccines. It is crucial to consider this form of prophylactic vaccine in a different light since the participants engaged in studies will be healthy, as opposed to those getting cancer vaccines. As a result, safety would be a greater issue in such scenario, mandating a bigger patient-safety group than would be required for a therapeutic vaccine administered in advanced cancer sufferers. Another issue to consider is that the uncertainty around the safety of a gene therapy product will be greater than that of, say, a peptide vaccine. Drug developers should perceive the lack of guidance for prophylactic cancer vaccines as a chance to influence regulatory decision-making rather than an obstacle. Regulators appreciate such early communication, which can take the shape of a meeting with the EMA's innovation task force (ITF). Although regulatory clearance is obliged, it does not promise the success with regards to patient access and reimbursement. Hence, considerations for rapid commercial utilization are essential. Consultation with Health Technology Assessment (HTA) bodies is indeed recommended to verify that endpoints specified by regulatory agencies are agreeable to both the payers and HTAs. In November 2011, the EMA organized a workshop on EMA/HTA-body parallel scientific guidance in drug development. The documents and presentations can be accessed from the EMA website. While this workshop is not indication-specific, the underlying conclusion is obvious; whatever the program, it is best to get early involvement of HTA/payer and regulatory authority. Such a strategy is likely to lower the chance of failure at the post-licensing reimbursement phase. Such collaborative consulting practices are also accessible at the national level, and in the UK, concurrent scientific advice conferences with MHRA and NICE are provided.

17.4 Personalized Cancer Vaccines

Owing to the emergence of next-generation sequencing (NGS) to recognize tumor mutations, the concept of developing vaccines capable of targeting specific tumor neoantigens was conceived. Complete exome sequencing of tumor as well as healthy cell DNA from specific patient is used to identify non-synonymous somatic mutations. The mutations are then graded based on their probability of manifestation and affinity adherence of the neoantigen to autologous MHC (major

histocompatibility complex) molecules, that may be anticipated with bioinformatic technologies such as NetMHCpan or IEDB (Ott et al. 2017; Sahin et al. 2017).

Since central tolerance is unlikely to remove cytotoxic T cell clones with high affinity for these antigen, neo-antigens arising from tumor specific mutations are strongly immunogenic. This strategy was tested in a phase 1 trial employing six patients who had melanoma of stage III and IV following surgical resection. Subcutaneous vaccination of synthetic long peptides designed to target up to 20 specific neoantigens per patient were administered, together with the TLR 3 and melanoma differentiation linked protein 5 agonist poly-ICLC as an immunostimulant. After 25 months of follow-up, four patients were free of tumor relapse (Ott et al. 2017). A phase 1 trial is now underway in glioblastoma individuals to probe a tailored personalized vaccine based on mutations. The vaccine is made up of numerous peptides that are tailored to individual patient's unique tumor sequence. The vaccine is administered following chemotherapy and radiation, during the temozolomide maintenance phase, and in tumor-treating fields (NCT03223103). Some other phase 1 trial is employing the personalized peptide vaccine strategy in individuals suffering from severe pancreatic colorectal or pancreatic cancer in conjunction with the checkpoint inhibitor pembrolizumab (NCT02600949). The use of mRNA-based cancer vaccines is by far the most current approach (Pardi et al. 2018). The IVAC-mutanome trial, a phase 1 trial that involved 13 participants having late melanoma (Sahin et al. 2017). Ten mutations had been specified for each patient, and couple of synthetic RNA molecules encoding five (27 mer) peptides showing the position 14 mutation were produced in vitro. Following that, the RNA molecules were coupled to an MHC trafficking signal peptide for improved routing and presentation to MHC and injected into inguinal lymph nodes of the patients. IFN-ELISpot was used to assess immunogenicity in CD4+ and CD8+ T cells from both before and post-vaccination leukapheresis samples. Without in-vitro stimulation, blood responses to one-fifth of the mutations could be detected. Two of the five patients with advanced illness demonstrated clear vaccine-related responses. The removal of an individual's lymph node metastases verified the presence of vaccine-induced T cells specific to neoepitopes in the tumor (Sahin et al. 2017).

A phase 1 clinical trial is now underway in patients with solid tumors to investigate an intravenous preparation of an RNA-based personalized vaccine in conjunction with the PD-L1 specific drug atezolizumab (NCT03289962) (Liao and Zhang 2021).

17.5 Challenges in Personalized Vaccines

17.5.1 Selecting the Right Antigen: Improving Bioinformatics

Owing to the advent of parallel sequencing, a new era in antigen selection emerged. It is difficult to determine mutations that will have the greatest in vivo immunogenicity. Bioinformatic forecasting methods strive to rate antigen immunogenicity based on the expected epitope's binding affinity to molecules of MHC, the chances

of presentation, clonality, and the amount of expression of the related RNA. But subsequent studies revealed that CD8+ responses to predicted high-affinity binders were as low as 29%, highlighting the necessity of improved algorithms (Sahin et al. 2017).

17.5.2 Selecting the Right Combination

Because tumor cells have developed several immune escape strategies, combined therapies are required to re-establish anticancer immunity. Antigen release by tumor cell death can be aided by traditional approaches such as chemotherapy and radiation. By inhibiting the negative regulatory route employed by tumors, checkpoint inhibitors put a stop to endogenous T cells. They have demonstrated effectiveness across many cancer types on their own; however, less effectiveness was gained in tumors free of penetrating lymphocytes (Hegde et al. 2016). The absence of invading T cells may be due to cancer cells creating a tumor suppressive milieu via the production of immunosuppressive cytokines, recruitment of regulatory T cells, and MDSCs. An increased level of indoleamine-pyrrole 2,3-dioxygenase (IDO) expression in cancerous cells results in immunosuppression via depletion of tryptophan, that promotes T regulator cells (Elia et al. 2008; Moon et al. 2015; Braun et al. 2005). T cell migration via the vascular endothelium at the tumor site requires the expression of vascular adhesion molecules (VCAM-1) and intercellular adhesion molecules (ICAM-1). Angiogenic chemicals, such as vascular endothelial growth factor (VEGF), restrict endothelial adhesion molecule production and hence T cell movement in the tumor microenvironment (Bouzin et al. 2007; Motz and Coukos 2013). Combination therapy with TGF-ß inhibitors, VEGF inhibitors, or newer immunomodulators such as IDO inhibitors may be beneficial in overcoming the tumor-suppressive microenvironment and are now being studied in clinical investigations (NT02873962, NCT03347123, and NCT02423343) (Moon et al. 2015). Traditional chemotherapy, such as cyclophosphamide, can also be used to deplete Tregs.

17.5.3 Choosing the Right Time: Adjuvant Vs. Palliative

Tumor immunosuppression frequently corresponds to tumor burden, lowering the benefits of immunotherapy in patients with advanced illness. Immunologic responsiveness rates to vaccinations in clinical trials are frequently greater during adjuvant treatment than in palliative care, providing support for the use of vaccines at an initial phase of disease (Gulley et al. 2011). Moreover, existing personalized vaccine techniques are demanding, and the manufacturing duration of few months may be difficult for individuals with severe illness. Again, the combination approaches might be utilized to strike a balance between vaccine production and application.

17.5.4 Tumor Evolution and Loss of Antigen

Along with the tumor growth, additional mutations arise, that can render neo-epitope vaccines ineffective owing to mutation and loss of neoepitope's antigenicity (Ott et al. 2017; Sahin et al. 2017). T cells rely on processing and presentation of antigen via MHC proteins to recognize targets. Downregulation of MHC class I proteins in cancerous cells leads to diminished antigen presentation, which favors immune evasion (Seliger et al. 2001). MHC class I protein downregulation is seen in a variety of cancer types. It can occur either genetically or because of a protein synthesis deficiency (Reeves and James 2017). Antigens are normally broken into the fragments of peptide by immunoproteasomes in the cytoplasm of cells in order to ensure their attachment to MHC class I. Downregulation of proteasome complex subunits has been correlated to tumor proliferation and metastasis. The endoplasmic reticulum is where tiny peptide fragments are coupled to MHC class I. A deficiency in the antigen processing associated transporters (TAP) in the endoplasmic reticulum or a loss of the endoplasmic aminopeptidases (ERAP 1 and ERAP2) can lead to even lower antigen expression (Mehta et al. 2009) (Table 17.1).

17.6 Conclusion

The reported success stories of vaccines have provided an explosion of rejuvenation approaches like tailored approaches and renewing of techniques specifically for vaccine development. But till date, there is no vaccine in market that act as pillar to neutralize progression of cancer. Many clinical trials at early stages indicate the potential of vaccines. Furthermore, advancement in molecular techniques has paved way for much advanced protocol designing and preparation of target-based vaccines. Hopefully, the next decade expects to provide market with high throughput vaccines that will act as boon to eradicate the mass tumor cases. Further advancements are required for precision-based prediction about modeling, algorithms, and simulation factors. This era must focus on the development of validated simplified complex models for pharmacological platforms that play a rational role in acceptance of these vaccines. Overcoming of these hurdles will pave a way for optimized vaccine with a tagline of "one short to curb cancer menace."

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Table 17.1 Cancer vaccines in clinical development

Clinicaltrials.gov identifier	Phase of study	Type of cancer	Treatment	Mode of action
NCT03328026	Phase 2	Breast carcinoma	Intradermal SV-BR-1-GM, ipilumab, interferon, cyclophosphamide, pembrolizumab	Vaccine containing cells secreting GM-CSF, anti-CLTA-4, cytokine, chemotherapy, anti-PD-1
NCT03152565	Phase1/2	Colorectal cancer	Autologous dendritic cell (ADC) (intradermal) in combination with avelumab	ADC vaccine, anti-PD-1
NCT03029403	Phase 2	Fallopian tube cancer, epithelial ovarian carcinoma	DPX survivac (subcutaneous), Pembrolizumab, cyclophosphamide	Peptide vaccine targeting surviving, anti-PD-1, chemotherapy
NCT02499835	Phase-1	Carcinoma of prostate	pTVG-HP (intradermal), Pembrolizumab	pTVG-HP plasmid DNA vaccine encoding prostatic acid phosphate, anti-PD-1
NCT03164772	Phase 1/2	Non-small cell lung cancer	BI 1361849 (intradermal), Durvalumab alone or in combination with tremelimumab	m-RNA vaccine, Anti-PD-1, anti-CLTA-4
NCT03406715	Phase 2	Small cell lung cancer	Ad.p53-DC (intradermal) in combination with ipilimumab and nivolumab	Autologous dendritic cell based p53 vaccine, anti-CLTA-4, anti-PD-1
NCT03289962	Phase 1	Solid tumors	RO7198457 (intravenous), atezolizumab	Personalized RNA mutanome vaccine, anti-PD-L1
NCT03162224	Phase 1/2	Head and neck cancer	MEDI0457 (intramuscular), Durvalumab	HPV DNA vaccine, anti-PD-L1
NCT03260023	Phase 1/2	HPV related carcinoma	TG4001 (subcutaneous), Avelumab	Anakinra virus vaccinia encoding IL-2 and HPV-16, anti-PD-L1
NCT02451982	Phase 2	Pancreatic adenocarcinoma	GVAX (intradermal), Cyclophosphamide alone or in combination with nivolumab	Vaccine based on whole tumor cell secreting GM-CSF, chemotherapy, anti-PD-1

(continued)

Table 17.1 (continued)

Clinicaltrials.gov identifier	Phase of study	Type of cancer	Treatment	Mode of action
NCT03047928	Phase 1/2	Metastatic melanoma	PD-L1/IDO vaccine (subcutaneous), nivolumab	Peptide vaccine, anti-PD-1
NCT02808143	Phase 1	Bladder carcinoma	Pembrolizumab, BCG	BCG, anti-PD-1
NCT03199040	Phase 1	Triple negative breast cancer	DNA vaccine (intramuscular) individually or with durvalumab	DNA vaccine, anti-PD-L1

Note. The data shown in following table have been retrieved from https://clinicaltrials.gov

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