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FOCUS: VACCINES

Anti-Cancer Vaccines — A One-Hit Wonder?

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Immunization against common bacterial and viral diseases has helped prevent millions of deaths worldwide. More recently, the concept of vaccination has been developed into a potentially novel strategy to treat and prevent cancer formation, progression, and spread. Over the past few years, a handful of anti-cancer vaccines have been licensed and approved for use in clinical practice, thus providing a breakthrough in the field. However, the path has not always been easy, with many hurdles that have had to be overcome in order to reach this point. Nevertheless, with more anti-cancer vaccines currently in development, there is still hope that they can eventually become routine tools used in the treatment and prevention of cancer in the future. This review will discuss in detail both types of anti-cancer vaccine presently used in clinical practice — therapeutic and preventive — before considering some of the more promising anti-cancer vaccines that are currently in development. Finally, the issue of side effects and the debate surrounding the overall cost-effectiveness of anti-cancer vaccines will be examined.

INTRODUCTION

Since the 1950s, the idea of a vaccination against cancer has developed from a fanciful hypothesis into a hard-lined reality that has captivated generations of cancer researchers with its ever-increasingly vast potential [1]. Arguably, one of the most attractive aspects of this branch of cancer immunotherapy, compared with all other treatments currently available for cancer

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†Abbreviations: HPV, human papilloma virus; CTL, cytotoxic T-lymphocyte; TSA, tumor-specific antigen; TAA, tumor-associated antigen; FDA, Food and Drug Administration; mCRPC, metastatic castration-resistant prostate cancer; PBMC, peripheral blood mononuclear cell; PAP, prostate acid phosphatase; GM-CSF, granulocyte-macrophage colony-stimulating factor; MHC, major histocompatibility complex; HLA, human leukocyte antigen; CDC, Centers for Disease Control and Prevention; MMR, measles, mumps, and rubella; HBV, hepatitis B virus; IL-2, interleukin 2; MUC-1, mucin 1; mAb, monoclonal antibody; Treg, regulatory T-cell; alum, aluminium salts; MPL, monophosphoryl lipid A; LPS, lipopolysaccharide; PAMP, pattern-associated molecular pattern; PRR, pattern recognition receptor; TLR4, Toll-like receptor 4; NICE, National Institute of Clinical Excellence; QALY, quality-adjusted life year.

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(e.g., surgery, chemotherapy, radiotherapy, small molecule inhibitors, monoclonal antibodies, etc.), is that, in theory, it is something that can be administered just once or over a short course with booster vaccinations (much like current vaccination programs against bacterial or viral infections) with minimal invasiveness and can potentially protect an individual against cancer for life [2].

In the past 60 years, a better understanding of the role of the immune system against cancer along with improving strategies for vaccine development have allowed for the creation of many potential vaccines against specific cancers, a few of which have been licensed for use in clinical practice with many more currently in phase II/III clinical trials [3]. Of the handful of anti-cancer vaccines currently being used in clinical practice, perhaps the most famous of these is a prophylactic vaccine that targets a subset of the human papilloma virus (HPV†), which causes cervical cancer. For its discovery and development, Harald zur Hausen was awarded the 2008 Nobel Prize in Physiology and Medicine, serving as a breakthrough moment and underlining the credibility of vaccination as a means of treating and preventing cancer [4].

Broadly speaking, anti-cancer vaccines can be divided into two types: therapeutic and preventive. Therapeutic vaccines are used to treat patients who already have cancer, whereas preventive vaccines (such as the HPV vaccine) are used to prevent cancer from occurring [5]. This review will explore examples of both therapeutic and preventive vaccines and will discuss the state of some of the new potential anti-cancer vaccines currently in development and some of the scientific and economic drawbacks of their use.

THERAPEUTIC ANTI-CANCER VACCINES

Rapid advancements in the understanding of the immune system and its role in cancer have allowed for the development of therapeutic vaccines that utilize the host's own immune system to essentially prime it to specifically target, attack, and kill tumor cells [6]. Central to this is the role of antigen-presenting cells (e.g., dendritic cells, etc.) and T-lymphocytes. $CD4^+$ T-lymphocytes release cytokines that prime and activate $CD8^+$ cytotoxic T-lymphocytes (CTLs) to kill tumor cells as part of cell-mediated immunity [7]. There are two types of tumor antigen that the immune system can target: tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs). TSAs are antigens specifically expressed on tumor cells, whereas TAAs are antigens that are more widely expressed on both tumor and host cells. The advantages of TSAs are that they are specific to the particular tumor and typically generate a greater immune response compared to TAAs. However, TSAs occur very rarely, and their identification in a specific tumor is often the limiting factor in the development of an anti-cancer vaccine that targets a TSA [8]. On the other hand, TAAs occur more commonly, although they usually generate a weaker immune response compared to TSAs. Anti-cancer vaccines targeting TAAs also carry a risk of autoimmunity [9].

To date, the only therapeutic anti-cancer vaccine that has been licensed for use in clinical practice is sipuleucel-T (Provenge), which is used for the treatment of prostate cancer. It was first licensed by the U.S. Food and Drug Administration (FDA) in 2010 for use in the treatment of asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) [10]. It involves an autologous cell transplant, whereby peripheral blood mononuclear cells (PBMCs) are taken from the patient and incubated with a fusion protein consisting of recombinant prostate acid phosphatase (PAP) (a TAA expressed in prostate tumor cells) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Dendritic cells in the PBMC sample take up PAP and express it as part of a major histocompatibility complex (MHC) on their cell surface, and GM-CSF is used as an adjuvant co-stimulant to activate the dendritic cells in order for them to be recognized by specific CTLs.

These specific CTLs are then activated themselves and can replicate to form a reservoir of CTLs against PAP. These CTLs are then used to form the sipuleucel-T vaccine, which is administered to the patient. One of the main advantages is that each vaccine is autologous to the patient and thus avoids human leukocyte antigen (HLA) mismatching, a major issue associated with tissue transplantation [11]. A phase III randomized controlled trial (IMPACT) was successful in demonstrating prolonged overall survival rates for patients with mCRPC vaccinated with sipuleucel-T compared to a placebo control group, although there were no significant differences between the two groups in time to cancer progression [12].

The milestone that sipuleucel-T has provided in the timeline of anti-cancer vaccine development should not be underestimated and really provides hope for further therapeutic anti-cancer vaccines making it into clinical practice in the future. With exciting new tools in biomedical research such as next-generation sequencing, more and more potential TSA and TAA candidates are now being identified with anti-cancer vaccines currently in various stages of clinical trials development and testing. Therefore, the question is: Can any of these new developments reach the milestone-setting heights of sipuleucel-T?

PREVENTIVE ANTI-CANCER VACCINES

The other major type of anti-cancer vaccine aims to prevent cancer from developing in the first place and is therefore prophylactic in nature. Currently, all of the licensed preventive anti-cancer vaccines used in clinical practice target virus-causing cancers (oncoviruses) [13]. The most common one is the HPV vaccine (Gardasil) that was first licensed by the FDA in 2006 and recommended for use in females between the ages of 9 and 26 for the prevention of cervical cancer along with various other HPV-associated cancers (e.g., vaginal cancers, vulvar cancers, anal cancers, HPV-induced oral cancers, etc.) [14]. Gardasil targets four specific subtypes of the HPV — 6, 11, 16 and 18 — of which HPV 16 and 18 cause about 70 percent of all cases of cervical cancer worldwide. Unlike sipuleucel-T, the HPV vaccine relies primarily on generating an antibody response to prevent initial HPV infection [15]. Data from phase III clinical trials indicate that the HPV vaccine protects against more than 90 percent of HPV infection caused by HPV 16 or 18 for females who had received three doses of the vaccine [16]. However, as the vaccine is not fully protective against all cases of cervical cancer, cervical screening still remains a vital tool for the detection and diagnosis of cervical cancer [17]. Moreover, as the HPV vaccine has only recently been introduced into clinical practice, issues surrounding its long-term safety and efficacy and debates about whether males should also receive it are yet to be fully addressed [18]. More recently, the U.S. Centers for Disease Control and Prevention (CDC) has also recommended the inclusion of Gardasil into the vaccination programs for males aged 11-12 [19]. Nevertheless, it remains to be seen whether other countries follow suit.

Another example of a preventive vaccine is the hepatitis B virus (HBV) vaccine that protects against chronic hepatitis B infection, which significantly increases the risk of hepatocellular carcinoma. Similar to the HPV vaccine, it relies on generating an antibody response to prevent the initial HBV infection [20]. Many countries worldwide have incorporated the HBV vaccine into their vaccination programs during childhood or adolescence. This has seen the rates of chronic HBV infection reduce significantly when three doses of the HBV vaccine were administered, especially in high-risk areas and groups [21]. For example, in the United Kingdom, pregnant mothers are routinely screened for HBV infection and a course of the HBV vaccine has been shown to prevent perinatal transmission of HBV to the baby in approximately 90 percent of cases [22].

In terms of vaccine safety, any issue with regard to potential long-term complications associated with a vaccine can have a serious and damaging impact on the rates of

vaccine uptake and coverage within a general population. A rather poignant example of this was the Wakefield scandal in the United Kingdom, in which a series of falsified results with regard to the measles, mumps, and rubella (MMR) vaccine led to an alleged link with autism (which has since been disproved) [23]. This view was largely perpetuated by the media, leading to a significant reduction in the uptake of the MMR vaccination causing a subsequent loss of coverage and, thus, a significant rise in the number of cases of measles, mumps, and rubella [24]. Although this was an extreme case and any lingering doubts surrounding the MMR vaccine have long since been disproved, the fallout from this saga sparked a negative change in public attitudes toward vaccines in general and their overall safety and had a knock-on effect on the rates of uptake of other vaccines from which the recovery is still taking place today. In fact, public concerns with regard to the safety of the MMR vaccine are similar to those that are often highlighted as part of the key reasons as to why patients refuse the HPV vaccine [25]. On top of this, a lack of information with regard to the long-term safety and efficacy of the vaccine only serves to further increase the confusion and distrust among members of the general population and health care workers [26]. Therefore, education of the general public and health care workers remains one of the key goals to ensuring sufficient long-term coverage of the general population against HPV.

Furthermore, the current business models employed by pharmaceutical companies involved in anti-cancer vaccine development are generally considered unsustainable in the long term as the costs of research and development often outweigh the profits gained from the marketing of anti-cancer vaccines. This leads to a vicious cycle where the lack of financial profit inevitably results in a lack of motivation to further develop new anti-cancer vaccines, which, in turn, significantly slows down anti-cancer vaccine research and development. Therefore, the role of the pharmaceutical industry cannot be underestimated, and new and more innovative business models are vital and need to be established in order to ensure a level of sustainability toward the future of anti-cancer vaccine development [27].

Viruses are the underlying cause in approximately 10 percent of all cases of cancer and are therefore an attractive therapeutic target for cancer prevention. Previous success with vaccines used to treat and prevent infectious diseases caused by viruses have provided a platform for identifying oncoviruses and utilizing the host immune system to effectively target and eliminate them. The biggest challenges currently facing preventive anti-cancer vaccines are clinical, social, and economic in nature. Debates are currently ongoing, and key decisions are still yet to be made with regard to how preventive anti-cancer vaccines can be delivered to a general population in an ethical and cost-effective manner (see discussion below).

PROMISING ANTI-CANCER VACCINES CURRENTLY IN DEVELOPMENT

While there are only a handful of anti-cancer vaccines currently available in clinical practice, over the years there have been many more that have been put through clinical trials, each with varying degrees of success and failure. One of the most advanced anti-cancer vaccines currently in development is the gp100 melanoma vaccine. This is a therapeutic vaccine containing an enhanced version of a TAA, gp100, which is expressed on the surface of melanoma tumor cells. A recent phase III clinical trial found that patients with advanced stage III/IV melanoma who received the vaccine along with standard interleukin 2 (IL-2) therapy had a significantly improved clinical response rate and longer progression-free survival compared to patients who were given IL-2 therapy only [28]. However, these results do not correlate with three independently conducted phase II trials examining similar endpoints [29], although these independent studies were all significantly underpowered. Therefore, further studies are warranted in order to fully establish the un-

derlying mechanism of action and the true efficacy of the vaccine.

Another promising anti-cancer vaccine that has recently generated a lot of interest is L-BLP25 (Stimuvax). This is another therapeutic vaccine that contains both CD4 and CD8 epitopes for a proteoglycan, mucin 1 (MUC-1), expressed on the cell surface of several tumor types [30]. Creating an anti-cancer vaccine that has a common target for various different cancers is clearly advantageous, not least from both a practical and cost-effectiveness point of view. Currently, two large ongoing phase III clinical trials (START and INSPIRE) are testing L-PLP25 for the treatment of non-small cell lung cancer [31].

One of the few types of anti-cancer vaccines currently in development for targeting TSAs is the anti-idiotype vaccine. These vaccines target specific antibodies on the surface of B-lymphoma cells in a personalized fashion. Therefore, each vaccine is unique to each patient and can be labor-intensive and costly to produce [32]. Additionally, several phase III clinical trials looking at the effects of anti-idiotype vaccines for the treatment of follicular lymphoma have shown mixed results. However, design flaws in each of the clinical trials have been noted and so anti-idiotype vaccines may still have a potential future yet [33]. While much of the research into anti-idiotype vaccines has focused on follicular lymphoma (a blood cancer), there has also been research looking at the generation of anti-idiotypic antibodies to treat a variety of solid tumors. The concept behind this strategy has been to generate second-generation monoclonal antibodies (mAbs) that are an exact mimic of the original TSA/TAA epitope (and a mirror image of the first-generation antibodies against the epitope). The advantage to this is that not only is the epitope present (on the antigen-binding site in the hypervariable region of the Fab fragment), but the constant region (Fc fragment) serves to modulate the immune response with greater effect [34]. There are presently several ongoing phase III clinical trials testing two different possible anti-idiotypic antibodies. Racotumomab is currently being tested against breast, lung, and possibly pediatric tumors [35], whereas abagovomab is being trialled in patients with ovarian cancer [36].

Along with sipuleucel-T, another anti-cancer vaccine called Prostvac is being developed to potentially treat prostate cancer. The target epitope is an enhanced form of prostate-specific antigen (PSA), a commonly used clinical biomarker for prostate cancer. Several phase II clinical trials concluded that Prostvac improved median overall survival rates and saw a significant reduction in the death rate in patients with mCRPC [37,38], with a phase III randomized trial still ongoing [3]. Interestingly, there have also been several clinical trials that have given Prostvac in combination with various chemotherapeutic or hormonal agents with promising results [39,40].

SIDE EFFECTS AND ECONOMIC DRAWBACKS OF ANTI-CANCER VACCINES

The obstacles currently standing in the way in the field of anti-cancer vaccines are both scientific and economical in nature. As our understanding of both cancer and the immune system progresses, new and seemingly more complex hurdles have to be overcome in order for potential therapies to be effective. One of the emerging characteristics of tumor cells is their level of flexibility and ability to adapt to a changing microenvironment [41]. It is now widely accepted that tumor cells take specific steps to evade the host immune system in order to survive and metastasize [42]. Specifically, the tumor microenvironment contains an abundance of negative regulators of the immune system, including regulatory T-cells (Tregs) that serve to down-regulate the immune response against anti-cancer vaccines [43].

In terms of drawbacks to the vaccines themselves, there have been side effects reported after vaccine administration. One of the biggest fears is the lack of selectivity of TAAs that can potentially lead to autoim-

munity occurring in the patient [9]. For example, cases of vitiligo (a condition that results in blotches of pigmentation loss in the skin) have been reported in patients receiving a melanoma vaccine [44,45]. This was believed to have been a side effect due to a lack of specificity of some of the targeted TAAs in the vaccine.

Another major issue is the use of adjuvants in the vaccine in order to amplify and potentiate the immunogenic effect. Adjuvants are vital for vaccine efficacy, but a fine balance must be struck between producing a desired effect and a toxic effect [46]. Examples of anti-cancer vaccine adjuvants currently approved for use in clinical practice include aluminium salts (alum), monophosphoryl lipid A (MPL) in an oil-in-water emulsion (known as MF59), and a combination of MPL and alum known as AS04 [47]. Alum and oil-in-water emulsions both act as a vehicle, delivering and controlling the release of the vaccine antigen to the host immune system. They can also directly stimulate the innate immune system through an inflammatory response, which, in turn, facilitates and amplifies a cell-mediated or humoral immune response [48]. MPL is derived from lipopolysaccharide (LPS), a pattern-associated molecular pattern (PAMP) recognized by a pattern recognition receptor (PRR), Toll-like receptor 4 (TLR4) [49]. AS04 is licensed for use as an adjuvant in Fendrix (a HBV vaccine) and Cervarix (a HPV vaccine) [50].

However, these established vaccine adjuvants are not without their drawbacks. Alum is very effective at inducing a Th2 antibody-mediated immune response, which is appropriate for both Fendrix and Cervarix as they are both virus-targeting vaccines, but not so much for therapeutic anti-cancer vaccines (which require a Th1 cell-mediated immune response). Also, alum-containing vaccines have been known to cause granuloma formation at the injection site with repeated administration. Both MPL and MF59 have production limitations that lead to cost issues and demand often outweighing supply [47]. Nonetheless, the recent approval and licensing of sipuleucel-T with its unique GM-CSF adjuvant has demonstrated renewed optimism, not just for new anti-cancer vaccine development but also for new vaccine adjuvant development as well.

There is currently an ongoing debate about exactly who should receive anti-cancer vaccines to prevent cancer from occurring over the course of the general population. In the case of the HPV vaccine, a general consensus has yet to be reached with regard to administering it to males. One of the main arguments against it is its lack of cost-effectiveness, and for this reason, it is not yet recommended by the National Institute of Clinical Excellence (NICE) [51]. Much of this notion stems from a series of biopsychosocial models that have been established to cross-examine the biological and economic impact of administering the HPV vaccine to males in a general population. In particular, a study conducted in the United States looking at the inclusion of males in the HPV vaccination program at the same time as females and its impact on the overall cost-effectiveness of the HPV vaccine demonstrated that by giving the HPV vaccine to preadolescent males (with 75 percent coverage), the costs regularly soared to over $100,000 per quality-adjusted life year (QALY) over a range of HPV-associated conditions and over $250,000 for cervical cancer alone. This is in stark contrast to vaccinating preadolescent females over a range of HPV-associated conditions (including cervical cancer) that regularly cost less than $50,000 per QALY (where $50,000 to $100,000 per QALY is generally deemed cost-effective) [52]. Furthermore, as increasing numbers of females are vaccinated against HPV, the overall coverage against HPV in the general population will increase with time. Therefore, there is an argument that with sufficient coverage in females (>75% coverage is generally considered satisfactory), this will provide adequate herd immunity to protect the male population as the overall number of cases of HPV fall with time [53]. However, whether or not exclusively vaccinating females against HPV will provide the hitherto protection and offset the cost of administering the HPV vaccine to the

general population in the long-term remains to be seen given that the biological implications of HPV to males still carries a very real risk. A more realistic strategy of HPV vaccination in males may be to target groups of those who are at higher risk. For example, a study in the United States performed a cost-effectiveness model analysis of targeted HPV vaccination in homosexual males and found that the cost of administering the HPV vaccine to this subgroup was indeed cost-effective (i.e., <$50,000 per QALY) for the prevention of genital warts and anal cancer [54]. This targeted approach would not be too dissimilar to the targeted vaccination regime already used for the HBV vaccine in the United Kingdom. The current practice in the United Kingdom is that the HBV vaccine is not included in childhood and adolescent vaccination programs and is therefore not routinely administered to the general population unless they are at high-risk (e.g., health care workers, laboratory staff, etc.) [55]. Nevertheless, the decision as to whether the administration of the HPV vaccine to males would be beneficial overall or not cannot entirely be based on financial sustenance alone and other factors such as ethical and psychosocial concerns cannot be ignored and also have to be taken into consideration [51], which only serves to complicate the issue further.

CONCLUSION

The notion of a vaccine that could be used to treat and offer lifelong protection against cancer has travelled a long path since it was first proposed. Along the way, many obstacles have had to be overcome and while there are still many hurdles in the way, the first few anti-cancer vaccines recently have made their way into clinical practice. Of this small handful, one is a therapeutic vaccine (sipuleucel-T) that is used to treat prostate cancer, whereas the others are preventive vaccines against virus-causing cancers. The licensing and approval of these vaccines has forged the way for other vaccines currently being developed and in various stages of clinical trials testing. There are currently many clinical trials looking at different anti-cancer vaccines, each with their own merits and flaws. A popular trend currently being trialled is combining anti-cancer vaccines with other chemotherapeutic agents and small molecule inhibitors, thus highlighting the huge strides that have been made in the development of new cancer treatments in this era of personalized therapy. With current major rapid advances in genetic sequencing and biomedical research, much effort is now being placed on the translation of the results obtained from laboratory experiments and clinical trials into developing more advanced and specialized drug targets for cancer treatment in clinical practice.

However, this does not come without new and additional obstacles that have yet to be overcome. For example, an increased perspective of the tumor microenvironment and how tumor cells evade the host immune system in order to survive and metastasize along with a greater understanding of how the immune system itself is kept in check through negative regulation poses additional questions for anti-cancer vaccines in the future. Also, the issue of side effects is something that has to seriously be considered as this arguably poses one of the greatest dangers of all. Finally from an economic standpoint, there is the issue of cost-effectiveness and the use of preventive vaccines to prevent specific cancers from occurring in the general population. There have been calls for males to be given the HPV vaccine, but more time is required to assess the true efficacy of the HPV vaccine currently given to a specific subset of the female population. This also poses the more general question of ultimately weighing the financial burden of cancer against that of the cost of vaccinating the general population against cancer.

Overall, the state of anti-cancer vaccines looks promising. With a few anti-cancer vaccines currently in clinical practice and several more currently in phase III clinical trials, the future certainly looks bright for the once much-maligned concept. The question however still remains: Has a revolution truly begun or are anti-cancer vaccines just a one-hit wonder?

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