Therapeutic Cancer Vaccines: Past Situation and Current Developments

Irina Luceska
Health Insurance Fund of Macedonia, Pharmacy Department, Skopje, Republic of Macedonia

Key words:
Vaccines; immunotherapeutics; cancer; autologous; generalised.

Correspondence:
Irina Luceska
Health Insurance Fund of Macedonia, Pharmacy Department, Skopje, Republic of Macedonia
E-mail: irina.luceska@gmail.com

Received: 02-May-2009
Revised: 01-Aug-2009
Accepted: 11-Aug-2009
Online first: 14-Aug-2009

Abstract
Therapeutic vaccines represent an option for active immunotherapy of cancers. The immunotherapy of cancer has been practiced already in the 19th century. With the advances in the fields of immunology, genomics and production technologies, it started to be accepted as an attractive investment option among the innovators. The early trends in the development of cancer vaccines, or immunotherapeutics, as referred to by some professional circles, were towards the autologous or personalized products, while recently they shift more towards the generalized types of vaccines. Number of various different antigens and adjuvants are used in the design of cancer vaccines. There is a small portfolio of already registered and commercialized cancer therapeutic vaccines, but the pipeline of Phase II and III products looks promising. The accumulation of clinical expertise offers a hope for understanding of the mechanisms, therapeutic regimes, combinations with other therapies, and safety of the immunotherapeutics.

Introduction
Although the conservative definition of VACCINE as a "product that produces immunity, therefore protecting the body from the disease" (1), does not leave much space for the term "therapeutic vaccines", the wider definitions used by the professional community encompass the therapeutic aspect of these products. The US Department of Health and Human Services (2) defines the vaccine as "a product of weakened microorganism given for the prevention or treatment of infectious diseases" and the definition given by the American Cancer Society (3), which seems to be the most comprehensive and inclusive states that "a vaccine is a modified version of a germ or other substance related to a disease, usually given by injection. It is used to stimulate the immune system to bring about resistance to that disease for a period of time, or even permanently".

Unlike prevention vaccines who are generally administered to healthy individuals, the "therapeutic or treatment vaccines" are administered to sick or infected patients and are designed to strengthen the body's natural defenses – induce or augment immune response by immunological methods, against an agent/disease that have already developed. To bridge the terminological gap between "vaccines" and "treatment of diseases", the term "immunotherapeutics" has often been used.

While the past has been scarce with specific results in the field of treatment vaccines, both clinically and commercially, and for the previous couple of years there have been no registered therapeutic vaccines on the market (4, 5), it seems that the future is promising. According to an independent report from Datamonitor (4) there were 12 therapeutic vaccines in Phase III or Phase II/III trials and the
therapeutic vaccines development was heavily weighted towards cancer vaccines, which accounted for 60.6% of the 208 active pipeline projects in 2005. Although cancer is the therapeutic area mostly covered by the recent developments, there have also been early Phase I and Phase II developments related to: HIV (6); other infective diseases: Hepatitis C (7, 8), Helicobacter pilori (9), Hepatitis B (10), HPV (11); multiple sclerosis (copolimer 1 -glatiramer acetate) (12) and other autoimmune diseases; some early developments of vaccines for treatment of allergies (13); Alzheimer (10), osteoporosis, Creutzfeldt–Jakob disease, Huntington’s disease, post kala azar dermal leishmaniasis (14), nicotine addiction (15) etc.

The therapeutic cancer vaccines aim to induce a therapeutic immune response through the patient’s own immune system (active immunotherapy). The purpose of immunotherapy/cancer vaccines is to recognize the small differences between tumor cells and normal cells by their preferential expression of certain molecules (tumor antigens) and to direct the various effector mechanisms of the immune system to destroy tumor cells and spare normal cells (5). Therapeutic cancer vaccines may prevent further growth of existing cancers, the recurrence of treated cancers, or eliminate cancer cells not killed by prior treatments (16). As the researchers gain a better understanding of how cancer cells avoid detection by the immune system, the development of new strategies for stimulating a more powerful anti-cancer immune response seems a more realistic and feasible option for treating cancer.

Cancer and the Immune System - the Early Discovery

Coley’s Toxin (also called Coley’s vaccine or Mixed Bacterial Vaccine) is a mixture consisting of killed bacteria of the species Streptococcus pyogenes and Serratia marcescens named after its discoverer - Dr. William Coley (17). Dr. Coley worked in the second half of 19th century and had collected enough information to conclude that a severe infection with the Streptococcus pyogenes bacteria called erysipelas, could apparently lead to subsequent improvement in the cancer patient’s condition. He compared the success rates of cancer treatment to his day and found out that surgery had been much more effective previously, before the use of antiseptics, when the infections were normal side effect of the surgery (18).

Dr. Coley discovered that the human immune system could be stimulated through administration of killed bacterial infusions, and then be capable of tackling cancerous cells along with the infection (17). His clinical tests achieved numbers of remissions in patients with severe or terminal tumors. His work was however marginalized and looked upon with skepticism by most of the medical community members, which showed little interest in non-surgical approaches to the treatment of cancer. His results were also difficult to reproduce (19).

Coley’s Toxins were registered as a drug and manufactured by the US-based pharmaceutical company Parke-Davis at the beginning of the 20th century. In 1963, with the new stringent regulations on the safety of novel therapies coming to place, this product was assigned “new drug” status by the Food and Drug Administration (FDA), making the prescription of this kind of therapy outside of clinical trials in the U.S. illegal (20). In Germany its production under the name Vaccineurin was carried on until 1990, when it ceased to get re-approval (21). Still, even now there is a modality of use of this formulation under the name Coley’s fluid, mainly in clinical trials (20).

In the decades after Coley, the ability of the immune system to provoke “spontaneous” regressions has been reduced by the use of immunosuppressive therapies such as chemotherapy, radiation and antipyretics, as well as the reduction of infections by sterile surgical techniques and antibiotics (17). The fever and infections were something to be combated and not be used therapeutically.

Later in the course of the 20th century the conventional perception was that the immune system and cancer were two different things that had nothing to do with each other. “Cancer immunology” was considered an “oxymoron” and the above basic attitude to some extent still exists, despite the major scientific advances (22). As people gradually began to learn more about, and better understand the immune system and particularly to understand that the immune system is primarily trained to detect invading foreign organisms and compounds, so-called antigens, the perception was that, by definition, cancer cells were invisible to the immune system and that there was no such thing as “cancer antigens”. This was the undisputable scientific view all the way up to the 1970s (10).

The fever and other immunological defense mechanisms remain an important factor in combating cancer. The BCG is one similar example as the Coley’s toxin. Since 1998 it has been FDA approved
for intra-vesical use in some bladder carcinomas (23) and is used as a preferred regimen for adjuvant therapy for superficial bladder cancer in patients who are at high risk of disease progression and/or recurrence, and represents the treatment of choice for carcinoma in-situ. Although the precise mechanism of action of the BCG in bladder cancer is not fully discovered, it is known that “it induces granulomatous reaction at the local site of administration (the bladder wall) and leads to sloughing of the epithelium and destruction of cancer cells in superficial bladder cancer. Administration of BCG intravesically with the adherence of live, attenuated BCG organisms to the bladder mucosa and tumor cells appears to be important for the development of an antitumor immune response, which includes T-lymphocyte activation and cytokine release” (24, 25).

New Decade of Active Immunotherapy

The recent advances in the immunology, but also the technological developments in the production processes led to enhancing the hopes for the cancer treatment vaccines, after the period of stagnation and many clinical and commercial failures (4).

As the increase of efficacy and safety are the ultimate goals in the development of new treatment options, so is the case with the research in the field of therapeutic vaccines. The specificity, as an inherited hallmark to the immune system, offers a window of opportunity for increase of the safety of the cancer immunotherapy. This should be achieved by selection of antigens which are selectively expressed by tumor cells, but not by normal cells i.e. tumor specific antigens (26). “Vaccines intended to prevent or treat cancer appear to have safety profiles comparable to those of traditional vaccines”, with the side effects being most often only mild. Rarely, like any other medication affecting the immune system, they can cause more severe side effects, like hypersensitivity or asthma (16).

It has been discovered that the immunological response to the tumor antigens is mediated by the cytolytic T-lymphocytes (CTL). The tumor antigens on the target cells which are recognized by the CTL are in a form of HLA-peptide complexes, composed of an antigenic peptide derived from any protein synthesized within the cell and HLA class I presenting molecule (27, 28). Some of the antigens used in cancer vaccines are: carcinoembryonic antigen, ganglioside molecules, heat shock proteins, MART-1, MUC1, NY-ESO-1, prostate specific antigen, Sialyl Tn, telomerase, tyrosinase etc. There is no tumor-specific antigen that is present on all tumors (16).

There are different approaches used for the delivery of the antigen in the cancer vaccines: whole-cell vaccines (tumor), gene modified cancer vaccines, dendritic cell cancer vaccines, peptide or recombinant protein vaccines, bacterial / viral vector vaccines, DNA cancer vaccines, anti-idiotypic vaccines. After vaccination, the delivered antigen is taken up by antigen-presenting cells, of which the most important are the dendritic cells. In their mature state the dendritic cells can trigger the T-cell response (29). The adjuvants such as AS04, Bacillus Calmette Guerin, Interleukins, granulocyte monocye-colony stimulating factor, incomplete Freund’s adjuvant, Keyhole limpet hemocyanin, montanide ISA-51, QS-21 (16) are used in the formulation of the vaccines to ensure optimal antigen presentation, by mechanisms like inducing the maturation of the dendritic cells, or increasing the capture of the antigen by the antigen-presenting cells (30).

There are two types of therapeutic vaccines with regards to patient-specificity: the autologous (personalized, patient-specific) and the generalized (non-patient-specific, antigen-specific, synthetic). While the former are produced by the patient’s own tissue, the later are standardized, mass-produced products (16). Both of these types have their advantages and disadvantages. The patient-specific vaccines have the advantage to be formulated targeted for each patient and don’t require in-depth understanding of the exact antigens involved, while offering very good efficacy. The downfall is that the cost for their production is high and the manufacture is low-scale, the logistics is complicated, and there are concerns over sterility and more complex regulatory approval process. As the science is moving forward and the cancer immunology antigens are discovered, the field of non-patient-specific vaccines is widely opening, and provides a possibility for offering comparable efficacy as mass-produced products. This is most probably the key that will lead to the commercial success of the therapeutic vaccines in the future, and an explanation of the setbacks of the mostly autologous vaccine early production and development pipeline. The result is that as the time passes, the generalized vaccines dominate the pipeline more and more (4). Datamonitor believes that there is also an increasing trend in therapeutic vaccines development towards the use of multiple antigens (and adjuvants), to attack cancers from multiple angles. The generally low levels of side effects make this a viable option.
The big pharmaceutical companies get involved more and more in the research and development of therapeutic cancer vaccines. “Antigen-Specific Cancer Immunotherapeutics” (ASCI) is the term used by Glaxo Smith Kline (GSK), referring to their particular approach in the development of cancer vaccines. ASCI are composed of a well-characterized tumor antigen, delivered as a recombinant protein, and combined with a GSK proprietary potent immunological Adjuvant System. “ASCI is intended to target different antigens expressed by a wide range of tumors, including non-small cell lung cancer (NSCLC), melanoma, breast cancer, head and neck cancer, bladder cancer and liver cancer. The expression of a single antigen in different tumor types (shared antigen) may allow for one ASCI to be used in the treatment of different tumors” (28).

The list of already registered and launched therapeutic vaccines is pretty short. These products are registered only in small number of countries, mainly as orphan designated products. Orphan drug designation is a special status of a product to treat a rare disease or condition, upon request of a sponsor and it qualifies the sponsor of the product for the tax credit and marketing incentives - exclusive marketing rights, research funding, a waiver from the application user fee (31, 32).

Table 1 reviews the therapeutic vaccines already registered (FDA referenced mainly), and some of the Phase II and Phase III developments (the list is not exhaustive).

**Table 1: Therapeutic cancer vaccines.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Type / technology</th>
<th>Treatment area</th>
<th>Registrations / development status</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>TICE BCG</td>
<td>Live attenuated (29)</td>
<td>Bladder cancer</td>
<td>FDA Approved (24)</td>
<td>Organon</td>
</tr>
<tr>
<td>M-Vax</td>
<td>AC Vaccine Technology + Autologous Cell (33)</td>
<td>Melanomas (34)</td>
<td>Phase II (7), FDA Approval as orphan designated product (33) since 1999; Approved in Switzerland since 2005 (35)</td>
<td>AVAX Technologies</td>
</tr>
<tr>
<td>D-Vax</td>
<td>Adjunctive treatment of ovarian cancer (34)</td>
<td>Phase II; FDA Approval as orphan designated product (34) since 2000</td>
<td>AVAX Technologies</td>
<td></td>
</tr>
<tr>
<td>LungVac</td>
<td>Non Small Cell Lung Cancer (33)</td>
<td>Phase I (6)</td>
<td>Vaxogenex</td>
<td></td>
</tr>
<tr>
<td>Oncovax</td>
<td>Autologous (36)</td>
<td>Prevention of recurrence in colon cancer after surgery (36)</td>
<td>Registration in Switzerland as of November 2008, and commercially available in other European countries; Fast track status by FDA (36)</td>
<td>AVAX Technologies</td>
</tr>
<tr>
<td>Oncophage (Vilapogen)</td>
<td>Autologous (37)</td>
<td>Metastatic melanoma (38); Renal cell carcinoma (34); Brain Cancer</td>
<td>Phase II; FDA Approval as orphan designated product (34) and for support to Russia; European designation as orphan drug</td>
<td>Antigenix</td>
</tr>
<tr>
<td>DCVax-Prolate</td>
<td>Autologous (identical cell vaccine) (39)</td>
<td>Prostate cancer</td>
<td>Phase III</td>
<td>Northwest Biotherapeutics</td>
</tr>
<tr>
<td>DCVax-Brain</td>
<td>Primary brain malignant cancer (34)</td>
<td>Phase III</td>
<td>Northwest Biotherapeutics</td>
<td></td>
</tr>
<tr>
<td>TVAX Immunotherapy</td>
<td>Autologous (identical cells) (40)</td>
<td>Primary central nervous system malignancies (34) and renal cell carcinoma</td>
<td>Phase II; FDA Approval as orphan designated product (34) since April 2007</td>
<td>TVAX Biomedical</td>
</tr>
<tr>
<td>Melacine</td>
<td>Generalized melanoma tumor cells treated combined with the adjuvant DETOX (41)</td>
<td>Metastatic melanoma (41)</td>
<td>Phase III (6)</td>
<td>GSK (originally by Corixa)</td>
</tr>
<tr>
<td>MAG-TEA</td>
<td>Recombinant protein (28)</td>
<td>NSCLC (36)</td>
<td>Phase III</td>
<td>GSK</td>
</tr>
<tr>
<td>Provance (Slopevac-T)</td>
<td>Autologous (antigen presenting cells) (42)</td>
<td>Asymptomatic, metastatic, androgen independent prostate cancer (42)</td>
<td>Phase II (6); late stage development – approaching commercialization (42)</td>
<td>Dendreon</td>
</tr>
<tr>
<td>SImuVax</td>
<td>Generalized – liposomal (6)</td>
<td>Unresectable stage II NSCLC (6)</td>
<td>Phase III (6) (43)</td>
<td>Merck Serono</td>
</tr>
<tr>
<td>Telomerase positive vaccine (SV1001)</td>
<td>Generalized (Telomerase vaccine) (10)</td>
<td>Locally Advanced and Metastatic Pancreatic Cancer (6)</td>
<td>Phase III (6) – TELOVAC trial</td>
<td>Pharmacia Hepatocellular carcinoma (6)</td>
</tr>
<tr>
<td>Allovect-X</td>
<td>Generalized – DNA (44)</td>
<td>Stage II or IV metastatic melanoma (44)</td>
<td>Phase II (6); FDA approval as orphan designated product (34) since 1999</td>
<td>Vical</td>
</tr>
<tr>
<td>TroVax</td>
<td>Generalized (Proprietary tumor associated antigen ST4, delivered by viral vector) (45)</td>
<td>Renal Cancer, Prostate, colorectal cancer (6)</td>
<td>Phase III</td>
<td>Oxford Biomedica in collaboration with Sanofi-Aventis</td>
</tr>
<tr>
<td>TG 4001/R3484</td>
<td>Generalized – recombinant virus</td>
<td>CIN II / III</td>
<td></td>
<td>Transgene in collaboration with Roche</td>
</tr>
<tr>
<td>TG 1042</td>
<td>Generalized – virus type</td>
<td>Cutaneous B-cell Lymphoma (47)</td>
<td>Phase II (47) (6)</td>
<td>Avaxix</td>
</tr>
<tr>
<td>TG 4010</td>
<td>Generalized – recombinant vaccinia virus</td>
<td>NSCLC (47)</td>
<td></td>
<td>Avaxix</td>
</tr>
</tbody>
</table>

**Conclusion**

The development of therapeutic vaccines, as an option for active immunotherapy of diseases, has been identified as being significantly targeted towards the field of cancer. Although the relation between cancer and the immune system has been discovered and immunotherapy of cancer has been practiced already in the 19th century, it is only during this decade, with the advances in the fields of immunology, genomics and production technologies, that it started to be accepted as an attractive investment option among the innovators. The reasons for the belated developments in the field of immunotherapeutics, might lie in the lack of profound understanding of the relation between cancer and immunity, the expensive production technologies, the lack of acceptance of the vaccines as a therapeutic option by the practitioners, the conservative approaches of radiotherapy and surgery in the control of cancer etc. The early trends in the development of cancer vaccines were towards the autologous or personalized products, while recently they shift more and more towards the generalized types of vaccines. There are number of various different approaches, antigens and adjuvants used in the design of cancer vaccines. The list of already registered or provisionally registered and well commercialized cancer therapeutic vaccines is rather short, but the pipeline of...
Phase II and III products looks promising. The accumulation of clinical experience offers a real hope for understanding of the mechanisms, therapeutic regimes, and combinations with other therapies, adverse effects of the therapeutic cancer vaccines, and subsequent proper usage and acceptance by the professional community.

References


