Review Article **CODEN: AJPCFF** **ISSN: 2321 – 0915**

Asian Journal of Phytomedicine and Clinical Research

Journal home page: www.ajpcrjournal.com

SYNERGISTIC AND FUTURE APPROACH ON CANCER THERAPY-A COMMUNICATION

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ABSTRACT

Cancer, a family of diseases increasing at an alarming rate and have been found to exist in the every region of world today. Cancer kills almost every individual it affects and rarely gets treated by conventional ways. There are number of reasons and risk factors by which people get likely affected by this dreaded disease. The main reasons of cancer are smoking, dietary factors, lack of exercise, occupation, genetics, pollution, radiation, and even prescription drugs. Out of all the main causes of cancer, obesity and smoking are the leading causes. The person gets affected when the cells lose their control over normal cell cycle and proliferate uncontrollably in a manner to form an abnormal mass of cells. Since many types of cancers exist, anyone at any age has a risk of being diagnosed. In an effort for people to speed up the process of finding a cure for cancer, people came up with urban legends and myths to prevent or get rid of cancer. Many people began to believe that antiperspirants and sometimes the Canola oil, which is said by scientists to be one of the healthier food oils, was also once rumored to be toxic and cancer causing. Currently, various therapies including chemotherapy and radiotherapy are in vogue, but neither of them had been proved promising with subtle side effects. Scientists are in rush to find out and assessing new strategies in eradicating cancer. In this context, several studies have been conducted, exploring the innovative innovations and new strategies in combating cancer. The main emphasis is laid on the treatment by vaccines, which makes them potential candidate in the development of new anti-cancer therapy.

KEYWORDS

Cancer, Treatment and Vaccines.

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INTRODUCTION

In this time of constant innovation where we are always looking over the horizon for the next major advance that will change the world, it can be hard at times to remain excited about the things we have already discovered. And this seems particularly so when it comes to something like cancer.

Yet, excited is just how we should feel when it comes to what we currently know about preventing cancer. With the powerful

Evidence that we have right now, today we could prevent 50 percent or more of all cancer in the United States and a large proportion of cancer globally[1-3]. And these numbers are not based on obscure, complicated steps. In fact, many health guidelines currently support the basic messages that can cut our risk of cancer in half, and the risk of heart disease, stroke, and diabetes even more. To demonstrate the promise of cancer prevention today, let's celebrate some of what we know.

This communication will address two issues: first is the question of whether cancer will exist in the future and, second, if the answer is "yes," what changes in cancer treatment and management are likely to be implemented? As discussed earlier regarding many signaling pathways and parameters, hold potential for reducing the incidence of some cancers in the future[3,4]. Overall, however, evidence suggests that cancer will "always be around" because mutation underlies carcinogenesis and we cannot escape from mutations. Although we may be able to avoid certain carcinogenic agents (e.g. tobacco) and processes (e.g. sunbathing), we certainly cannot avoid all of them. Furthermore, cancer is associated with aging and life expectancies are increasing[4]. As a consequence of people living longer, the incidence of cancer is increasing. However, maybe there is a lesson to be learnt from the history of medicine. In the past, there were dreaded infectious diseases, such as smallpox, which are now curable through vaccination. Could vaccination be used to eradicate cancer? The observation that the immune system could recognize and respond to tumors following bacterial infection was made over 100 years ago. As well known effector cells of the immune system can recognize tumor-associated antigens and kill tumor cells. This endogenous mechanism of protection against tumor cells by the immune system, called immune-surveillance, suggests that boosting the immune system by vaccination against tumor cells may be possible[3,5]. Alternatively, if we are not able to eradicate cancer, what will it be like having cancer in future decades? It is envisaged that cancer, a disease of the genome at the cellular level, will be detected much earlier than is possible today because of the rise of genomics and associated technologies and improvements in imaging. Many cancers may become a long-term, chronic disease (like arthritis) not linked imminently with death, as it was viewed in the past[6]. Although a cure is preferred, the complexity of cancer may foster the development of treatments that allow people to live more comfortably with the disease rather than cure it. In this chapter, we will examine current, far-reaching advancements in the fields of immunology and technology in order to form an educated prediction of the future of cancer.

Cancer vaccines

Our ability to harness the immune system to prevent and/or kill tumor cells is becoming evident[7-9]. Vaccination is called active immunization because it tries to stimulate the individual's own immune effector cells. A vaccine is composed of antigen(s) and adjuvant(s). Adjuvants are vaccine additives that enhance the immune response to an antigen. This contrasts passive immunization,

which involves the transfer of effectors of the immune system, such as T cells or secreted products of lymphoid cells, into the patient. Here, we focus on vaccinations. Cancer vaccines can either be designed to stimulate the immune system in order to cause tumor regression in a patient with cancer, a therapeutic vaccine or they can prepare the immune system prior to getting cancer for cancer prevention, so-called prophylactic vaccines[10-13]. Most cancer vaccines are designed to be therapeutic vaccines, though we will consider both types here.

Therapeutic vaccines

The production of a vaccine involves the selection of an appropriate antigen that will stimulate an effective anti-tumor response. Tumor-associated antigens may be derived from either degradation and processing of unfolded intracellular proteins that are shuttled to the surface of the tumor cell or from damaged or dying tumor cells. These may

include oncoproteins arising from oncogenic mutations or chromosomal translocations[14]. As T cells are the main effectors of an anti-tumor response, antigens from the vaccine must be displayed eventually on the surface of other cells, called antigen-presenting cells. A series of cellular events characterize an immune response upon administration of a cancer vaccination. Antigen-presenting cells, such as dendritic cells that reside in the tissue, are at the heart of signaling for the mission of eliciting T-cell mediated immunity. It is the dendritic cells that (1) acquire and (2) process the antigens, and, upon maturation, migrate to the lymphoid organs to (3) present the antigens to the main effector T cells. The uptake of antigens by the dendritic cells is primarily by endocytosis. Antigen processing involves cleavage of the antigen into small peptides by proteases. The adjuvant in a cancer vaccine induces the maturation of the antigen-presenting cells and their migration to the lymphoid organs. Processed antigen is translocated to the cell surface for presentation in association with proteins from the major histocompatibility complex (MHC; details of which are beyond the scope of this communication). It is the CD8+ cytotoxic T cells that recognize the antigen on the tumor cell membrane and proceed to kill the tumor cells by releasing cytotoxic granules or inducing apoptosis. Cancer vaccines are required to overcome tumor protective mechanisms.

Whole-cell vaccines

Vaccines against infectious diseases are composed of bacteria or viruses whose ability to produce disease has been reduced or attenuated by different processes, such as passage through an unnatural host, chemical treatment, or irradiation[15,16]. The first cancer vaccines were composed of irradiated tumor cells, being modeled after successful, attenuated pathogen vaccines. All of the antigens expressed by a specific tumor are included in the whole-cell vaccine design. These first cancer vaccines demonstrated immune responses in mouse models but were disappointing in clinical trials, causing either a weak response from the immune system (a weak immunogenic response) or a response against normal cells (autoimmunity)[15-17]. This may be because of the under-representation of immunogenic antigens relative to the total number of antigens and stimulation against normal gene products, respectively. For example, vitiligo, an autoimmune disease that targets melanocytes, was observed in studies of a melanoma vaccine, suggesting that the induced immune response also targeted normal antigens and thus normal cells. Some modifications of whole-cell vaccines are being pursued. For example, gene-modified tumor cells that express stimulatory molecules for T cells double as antigens and adjuvants. However, regardless of their degree of success, whole-cell vaccines have been important stepping-stones towards antigen-specific vaccines.

Peptide-based vaccines

Another strategy for the development of cancer vaccines is to use tumor associated antigens to generate an immune response. This involves the identification and characterization of specific molecules on the tumor cells that are recognized by T cells rather than using whole cells from tumors, as was known earlier[18]. Tumor-specific antigen molecules have qualitative or quantitative differential expression patterns in tumor cells compared with normal cells. Many of these antigens elicit an immunogenic response without autoimmunity. This has led to the production of antigen-specific peptide vaccinations. The peptides used are short sequences of amino acids that code for a part of the tumor-associated antigen and can be produced as synthetic or recombinant proteins. A growing list of breast tumor antigens, including HER2, mucin1, and carcino-embryonic antigen (CEA), provide the basis for the production of breast cancer vaccines. Several melanoma tumor antigens have also been characterized. A peptide-based vaccine targeting the melanoma-associated antigen glycoprotein 100 (gp100) has been developed to treat melanoma patients. The gp100 antigen is an antigen that is expressed in normal melanocytes, melanomas, and pigmented retinal cells. The gp100 peptide vaccine, along with interleukin-2, has been examined in a Phase III

clinical trial, and Rosenberg and colleagues reported a higher response rate than interleukin-2 alone.

Dendritic cell vaccines

Vaccines may also be composed of human dendritic cells, cells that are critical antigen-presenting and stimulatory cells for the induction of a T-cell-dependent immune response. Dendritic cells originate in the bone marrow, and reside in an immature state in peripheral tissues. As learned earlier, upon receiving inflammatory signals, they differentiate or mature and migrate to lymph nodes where antigens are presented and the T-cell response is initiated. *In vivo*, tumors secrete several factors that suppress dendritic cell differentiation and migration, and may contribute to the immune-suppression observed in cancer patients[15,18]. For the purpose of vaccination, dendritic cells must be isolated from an individual patient and cultured *in vitro* during which time they can be loaded or pulsed with specific antigens, DNA, or RNA via their high capacity for endocytosis (or other means of transfection such as electroporation). Subsequently, they are reintroduced into the patient. Thus, dendritic vaccines are labor intensive and expensive. Initial clinical trials using loaded dendritic cells have shown positive clinical responses and no significant toxicity. An antigen-loaded dendritic cell vaccine called Provenge™ (sipuleucel-T, Dendreon Corporation, Seattle, WA) was produced for the treatment of prostate cancer by the following steps:

(1) a dendritic cell precursor-enriched fraction was isolated (2) the cells were matured *in vitro* by incubation with a recombinant fusion protein (consisting of prostatic acid phosphatase linked to granulocyte– macrophage colony-stimulating factor (GM-CSF)) that targets the GMCSF receptor present on dendritic cells (3) the mature dendritic cells, now carrying the prostate cancer antigen, are administered.

Vaccines for cancer prevention

The therapeutic vaccines previously discussed are aimed at the tumor. Vaccines generated from shared tumor antigens have been successful as prophylactic vaccines in animal models but have not been tested in humans. However, there are a few select types of cancer that are caused by pathogenic carcinogens (i.e. bacteria or viruses), and in these cases conventional prophylactic vaccines that target the pathogen can be produced. Human papilloma virus (HPV) is the causative factor of cervical cancer; that is, cervical cancer is 100% attributable to viral infection. The recent approval of vaccines against several HPV strains will prevent a large proportion of deaths caused by cervical cancer in the near future. Large strides are being made in the development of prophylactic vaccines for breast cancer. As mentioned earlier, several promising breast cancer antigens have been characterized. Prophylactic breast cancer vaccines are likely to be an important alternative to prophylactic mastectomies and/or oophorectomies or chemoprevention in women who carry germ-line mutations in the *BRCA1* and *BRCA2* genes. Safety and immune responses have been demonstrated for therapeutic vaccines in several Phase I and II trials in patients with breast cancer but prophylactic trials are needed[18,19]. Reluctance to carry out large-scale trials comes from the fear of autoimmunity against normal breast tissue, though autoimmune attack of normal breast tissue may be tolerable and may not have more severe consequences than mastectomies.

Hurdles to jump

There are several problems that need to be overcome for the full potential of vaccine development to be reached. First, the immune system becomes less effective with aging and is suppressed by conventional chemotherapy. It is rare that pre-clinical studies are performed in old mice or mice that have been pre-treated with chemotherapy and this may help to explain the discrepancies between outcomes in mice and humans; positive immunological responses in mice are often not reproducible in humans. It may be that therapeutic cancer vaccines may be more successful in pediatric cancer patients than older patients. Such comparisons need to be carried out. Second, many vaccines may be most effective in early stage cancer patients, although trials using such patients

are unlikely to receive approval. In addition, resistance against therapeutic vaccines may arise. Antigen-negative tumor cell clones evolve as a result of selective pressure exerted by the vaccine. Mutations that alter antigen expression will allow tumor cells to evade the immune response and survive. Also, vaccines need to be tested in all appropriate contexts. Vaccines against tumor-specific antigens are being tested in humans exclusively as therapeutic agents, and not as prophylactics, even though the success of these agents in pre-clinical trials has been demonstrated almost exclusively as prophylactics. Note that as human tumors can only be grown in immune-deprived mice (e.g. nude mice), immunotherapy studies on human tumors cannot be performed in existing pre-clinical models and results from animal models may be species-specific. We cannot assume that what is successful in mice will be successful in humans because some aspects of physiology between the two are different. Prophylactic vaccines aimed at tumor-specific antigens (not including those directed against pathogens, e.g. HPV) have not been tested in clinical trials because the test population will be healthy individuals and the consequences and/or side effects are unknown. However, at some point, vaccines as prophylactics need to be tested in humans.

Cancer nanotechnology

A multidisciplinary field that promises to make a huge impact on cancer in the future is cancer nanotechnology. Nanotechnology is the study of devices (or their essential components) that are made by humans and have at least one dimension in the 1-1000nm range. For scale, the size range is similar to the size of a few atoms to the size of sub cellular structures. Nanotechnology has many potential applications in the field of cancer and a selection of these applications will be briefly described here. The problem of targeting a cancer drug specifically to a tumor must be better addressed in the future. We are all aware of the harsh side-effects observed with conventional therapies which are a result of the exposure of healthy tissue to these agents. Nanostructures that can be filled with anticancer drugs and which also contain targeting moieties on their surface are called nanovectors. Nanovectors hold promise in accomplishing efficient tumor-specific drug delivery. Lipid-based nanovectors, called liposomes, and some are used in the clinic for treatment of Kaposi's sarcoma and breast cancer. In addition, nanovectors will be used as imaging contrast agents that greatly amplify signals detected by various imaging techniques. It is easy to envision that nanotechnology will refine microarrays to greater-capacity "nanoarrays". Lastly, and perhaps most uniquely, nanotechnology will lead to bio-molecular sensors that are able to detect many biomarkers simultaneously and will be used for refined diagnosis, prognosis, and treatment monitoring. Two specific designs, the nanocantilever and nanowires, currently show promise. Both can be coated with molecules that bind to biomarkers. Nanocantilevers are deflected upon binding to a biomarker (in a manner similar to piano keys when they are tapped). Lasers are used to detect the deflections. Nanowires undergo a change in conductance upon binding and this change is detected electronically. Both may change the way and speed at which cancer is monitored.

In summary, nanotechnology may enable specific cancer drug targeting, leading to better therapeutic results and fewer toxic side-effects. It promises to enhance imaging and biomarker detection for improved diagnosis. Used as bio-molecular sensors, this technology may replace the need for biopsies.

Are we making progress?

Do you think we are making progress? Despite several media articles that raise doubts, the real answer to this question is almost certainly "yes"! The statistics are available. For example, the overall survival for all stages of prostate cancer combined has increased from 67% to 89% over the past 20 years. The increased survival is attributable to both earlier and better detection, and advances in therapeutics. Furthermore, cancer death rates decreased in both men and women from 1998 through 2007 in the USA and similar progress has been reported in other parts of the world[19].

Although our knowledge about cancer has grown enormously, there is still so much more to learn. Perhaps there are some secrets held in the heart-literally. Primary cardiac tumors, of which only one-quarter are malignant, are rare (0.02%). Investigations into why cancer is rare in this particular tissue may lead to knowledge of protective mechanisms that can be applied to other tissues. Newly approved therapies, shown in Table No.1, are directed against molecules that are tyrosine kinases (e.g. EGFR, VEGFR, ABL). There are several tyrosine kinases that are known to play important roles in carcinogenesis (e.g. fibroblast growth factor receptor, FGFR) but inhibitors that target them, although in clinical trials, have yet to be approved. However, although we can design new cancer therapies against molecular targets, tumor cells may undergo additional mutations that can result in drug-resistant clones. This suggests that combinations of drugs and drug strategies are important for future treatment regimens. The report of the development of a "two-in-one" antibody that interacts with either HER2 or VEGF suggests that the way we administer treatment combinations may change. Also, a new type of gene therapy is on the horizon. The first in-human phase I clinical trial has demonstrated that systemic administration of siRNAs via targeted nanoparticles to patients with melanoma can reduce both a specific mRNA and its associated protein. This result may open the door to the development of gene-specific therapeutics. As we saw in previous chapters, there are many potential molecular strategies, such as angiogenesis inhibitors, anti-endocrine drugs, apoptotic inducers, cell cycle inhibitors, HDAC inhibitors, and inhibitors of cell renewal signaling pathways, in development. For many of these drugs, the therapeutic index is enhanced compared with conventional chemotherapies[17-19].

The big limitation of conventional therapies is the fact that cancer cells develop from the normal healthy cells makes the entire process of treatment a walk through hell. So, in order to kill cancer cells, there is no other choice but to introduce chemotherapy and radiotherapy which kills the healthy cells as well. These therapies are highly toxic as they destroy one human cell for every five to ten cancer cells and hence, the side effects are debilitating. However, deadly the disease has been, mankind has found a way and fought through it and it emerged victorious always. Let's believe the same will happen in our fight against cancer. We await the elongation of the list of newly approved molecular cancer therapeutics, some of which are shown in Table No.1.

Table No.1: A selection of targeted cancer therapeutics approved in 2011

S.No	Trademark	Drug	Description	Target	Cancer	Company
1	Avastin™	Bevacizumab	Humanized mAB	VEGF	Colorectal	Genentech
2	Erbitux™	Cetuximab	Humanized mAB	EGFR	Colorectal	Imclone
3	Gleevec™	Imatinib	Small-molecule inhibitor	BCR-ABL, KIT, PDGFR	CML, GIST	Novartis
4	Herceptin™	Trastuzumab	Humanized mAB	HER2	Breast	Genentech
5	Iressa™	Gefitinib	Small-molecule inhibitor	EGFR	NSCLC	AstraZeneca
6	Nexavar™	Sorafenib	Multi-kinase inhibitor	Raf, VEGFR, PDGFR, KIT, RET	Renal cell carcinoma	Bayer Pharm
7	Sprycel™	Dasatinib	Small-molecule inhibitor	BCR-ABL, Src family	Imatinib-resistant leukemias	Bristol-Myers squibb
8	Sutent™	Sunitinib	Small-molecule inhibitor	PDGFR, VEGFR, KIT	Renal cell carcinoma, GIST	Pfizer
9	Tarceva™	Erlotinib	Small-molecule inhibitor	EGFR	NSCLC, pancreatic	Genetch, OSI Pharm
10	Tykerb™	Lapatinib	Small-molecule inhibitor	EGFR, HER2	Breast	GlaxoSmithKline
11	Vectibix™	Panitumumab	Human mAB	EGFR	Colorectal	Amgen
12	Velcade™	Bortezomib	Proteasome inhibitor		Myeloma	Millennium Pharm
13	Xalkori™	Crizontinib	Small-molecule inhibitor	ALK gene fusion, MET	NSCLC with ALK-gene fusions	Pfizer
14	Yervoy™	Ipilmumab	Human mAB	CTLA-4	Melanoma	Bristol-Myers Pharm
15	Zactima™	Vandetanib	Small-molecule inhibitor	VEGFR, EGFR, RET	Orphan drug for rare types of thyroid cancer	AstraZeneca
16	Zelboraf™	Vemurafenib	Small-molecule inhibitor	BRAF	Melanoma	Genentech
17	Zolinza™	SAHA (suberoylanilide hydroxamic acid)	Small-molecule inhibitor	HDAC	Non-Hodgkin's lymphoma	Merck and Co.

Abbreviations: mAB, monoclonal antibodies, CML, chronic myelogenous leukemia, GIST, gastrointestinal stromal tumor; NSCLC, non-small-cell lung cancer.

CONCLUSION

In conclusion we end up with the result to minimize the use of conventional therapies because of their debilitating side effects. The use of cancer drugs in a synergistic approach in combination with novel vaccines will eradicate this dreaded disease entirely. Their negligible side effects and new way to target cancer is bewildering and provide scientists a kind of platform for bringing more effective and significant treatments in near future.

ACKNOWLEDGEMENT

The authors are sincerely thanks to the Department of Zoology, Government Boys Degree College Baramulla, Jammu and Kashir, India for providing the facilities to complete this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Tajamul Islam Shah and Zahoor Ahmad Lone. Synergistic and future approach on cancer therapy-a communication, *Asian Journal of Phytomedicine and Clinical Research,* 7(4), 2019, 189-196.