Tumor vaccination

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Technology and target group: Cancer vaccines are intended to stimulate the patient's own immune system to attack cancer cells. These vaccines can be used for both prophylactic and therapeutic purposes. The goal of prophylactic vaccination is to prevent cancer from appearing in the population. For the foreseeable future, prophylactic vaccines will probably be used only to a limited extent. Current research is targeted mainly at developing therapeutic vaccines that can reduce tumor volume or offer protection against relapse in patients who have had cancer already. The greatest progress in cancer vaccine research has been made in malignant melanoma, non-Hodgkin's lymphoma, multiple myeloma, and colon cancer.

Patient benefit: To date, only few results have been reported from early clinical trials, often based on very few patients. Tumor reduction has been noted in patients with non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphatic leukemia. Tumors in some patients with non-Hodgkin's lymphoma temporarily, but completely, disappeared after vaccination. A study of 38 patients with malignant myeloma showed a significant extension in the time to relapse, from 0.6 years to 1.6 years. Furthermore, the 3-year survival rate increased from 33 percent to 53 percent in the vaccinated group. A study of 254 patients with colon cancer showed in followup after 5 years that 20 percent of the vaccinated patients had relapsed compared to 32 percent in the control group.

Economic aspects: The costs for administering vaccines are estimated to be low since vaccination is delivered in ambulatory care settings. The initial prices for vaccines are estimated to be relatively high and will vary widely depending on the manufacturing process used. No information is available on the cost effectiveness of this method.

Scientific evidence: Tumor vaccination is an experimental treatment method under development and is used only within the framework of scientific studies. There is poor* documentation concerning the patient benefit of cancer vaccination. There is no* documentation describing the cost effectiveness of the method. No tumor vaccines have yet been approved for use in Sweden.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see "Grading of evidence".

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Technology

Research regarding cancer vaccines have been going on for many years. Only during the past 10 to 20 years, however, have applications emerged within clinical oncology. These applications include both vaccines for cancer treatment and prophylaxis against the onset of cancer. For the foreseeable future, it is likely that clinical prophylactic vaccination will be used only in exceptional cases except for hepatitis B vaccine in liver cancer and vaccine based on human papillomavirus (HPV) in cervical cancer.

Cancer vaccines are intended to stimulate the patient's own immune system to attack cancer cells. The procedure involves subcutaneous injection of a vaccine containing cancer cell antigens. An antigen-presenting cell (APC, dendritic cell) takes up the antigens in the vaccine. Antigen-loaded and -activated APC then initiates a complicated process that activates various parts of the immune system. Therapeutically, it is essential for powerful activation to take place in the particular types of cells and molecules that can damage and eliminate tumor cells. Several different possibilities to strengthen this aspect of the immunological response are known and are being developed. One of the greatest weaknesses with therapeutic vaccines is that the capacity for cancer patients to react against their tumors is often suppressed. Presumably, the functional capability of the immune system has to be restored before vaccines can have the effects intended. A pre-requisite for cancer vaccines to be therapeutically effective is that the tumor cells express cancer antigens. Furthermore, in order for the immune system to recognize and destroy them, cancer cells must be sufficiently different from normal cells. Several groups of cancer antigens have been identified and are the target of clinical trials. Researchers are using isolated, synthetically produced, antigens or patients' own tumor cells that are acquired surgically. Examples of synthetically produced tumor antigens include CEA, EpCAM, MAGE, tyrosinase, etc. Another option is to use products from the tumor cells (eg, tumor immunoglobulin produced by the tumor cells in lymphoma and myeloma) (Table 1).

It is not yet clear which type of vaccine preparation is best. The advantage of using patients' own tumor cells in producing vaccine is that various tumor antigens are represented in the vaccine. The trend, however, is toward specific, synthetically produced, cancer antigens. These can be produced as DNA, proteins, or peptides. The vaccine can also be mixed with the patient's dendritic cells (see above) that have been expanded outside of the body (ex vivo). This type of cell mixture potentially provides a more effective treatment than the vaccine alone. It appears that a single vaccination is insufficient, and that patients require repeated boosters of vaccine over a longer period. Furthermore, the vaccine needs to be complemented with immunostimulants that counteract the weakening of the immune reaction which often occurs. The immunostimulants also promotes generation of cells and molecules that have the capacity to damage and eliminate the tumor. Probably, treatment will consist of an initial treatment period with regular and frequent vaccination (induction period) followed by maintenance treatment every second to third month for several years (booster immunization).

Target group

Therapeutic vaccination

Current research focuses mainly on the development of therapeutic vaccines. The greatest progress in vaccine research has been made in the areas of malignant melanoma, non-Hodgkin's lymphoma, multiple myeloma, and colon cancer. In Sweden, these types of cancer appear in about 12 000 patients annually. From this group, approximately 4 000 patients would comprise the potential target group for vaccination.

Therapeutic cancer vaccines will probably play the greatest role in adjuvant treatment following tumor-reducing treatment (usually surgery) to prevent relapse. The immune system is best preserved when the tumor volume is low.

Reports to date, almost exclusively, come from early clinical vaccination trials (mainly phase I and phase II trials). Results from only a few isolated phase III trials have been reported.

Table 1. Summary of ongoing clinical trials addressing cancer vaccines

Disease	Type of cancer vaccine	Clinical stage
Melanoma	Tumor cell-based vaccines	Phase III (1 registered in Canada, MelaCinE)
	Peptides (MAGE, tyrosinase, gp100 etc)	Phase I–II
	Gangliosides	Phase II–III
non-Hodgkin's lymphoma	Tumor idiotypic	Phase II–III
Multiple myeloma	Tumor idiotypic	Phase I–III
Chronic lymphatic leukemia	Leukemia cell-based Tumor idotypic	Phase I
Colon cancer	Tumor cell-based EpCAM, CEA	Phase III Phase I–III
Pancreatic cancer	RAS, telomerase, gastrin etc	Phase I–III
Breast cancer	HER2/neu	Phase I

Prophylactic vaccination
Prophylactic treatment with cancer vaccines will probably be used only to a limited extent in Sweden. Vaccine based on human papillomavirus (HPV) for cervical cancer (see below) can be possible as well as suitable vaccination in families with hereditary colon polyposis (condition involving a very large number of polyps throughout colon with a high risk for cancer).

Relation to other technology

If the effects of cancer vaccines can be confirmed, there is a high probability that they will be used as a complementary method to other cancer therapies. It is likely that cancer vaccines will be used mainly as adjuvant treatment following local treatment, eg, surgery. However, it is also possible that they will be used in conjunction with chemotherapy in advanced disease.

Patient benefits

Individual-specific vaccines have been produced for non-Hodgkin's lymphoma (NHL). Vaccines have been developed from the immunoglobulin that is produced by the tumor cells and are mixed with dendritic cells. The tumor immunoglobulin alone has also been delivered with various immunostimulants. In most of the patients, the immune system developed the capability to destroy cancer cells. Tumor regression has been observed in established disease. Complete remission has also been observed. However, the studies have involved only a small number of patients. In one phase II trial, patients with follicular lymphoma in remission after chemotherapy were vaccinated with tumor derived immunoglobulin. Twenty patients were included in the study. Eleven patients had residual tumor cells in blood. In eight cases the tumor cells disappeared completely [1]. This study provides a basis for a large ongoing phase III trial of follicular NHL in remission following chemotherapy. The trial, which started in the autumn of 2000, will randomize just over 500 patients to vaccination and control groups.

The same vaccination principles used in NHL were also used with multiple myeloma, mainly in phase I and phase II trials. The percentage of patients in whom positive effects on the immune system were reported following vaccination varied among the studies, from 35 percent to 100 percent [7]. Both regression of the disease and extension of disease-free survival were noted. All of these studies included

a small number of patients. One phase III trial involving vaccination was started following high-dose chemotherapy and stem cell transplantation. This study is expected to conclude in 2006.

Tumor regression was also found in trials where a few patients with chronic lymphatic leukemia were vaccinated with leukemia cells [8].

The earliest vaccination trials were conducted on patients with malignant melanoma, and it was within the framework of these studies that the first cancer antigens were defined [2,3,4,6]. Two principles for production of vaccine have received the main focus of research. One of the principles involves using tumor cell-based vaccines. The advantage of this approach is that all of the different antigens can be utilized. The disadvantage is that the product cannot be standardized. An example of tumor cell-based vaccine in malignant melanoma is Melacine, a therapeutic vaccine registered in Canada for stage IV melanoma. In a small study (n=38), another type of tumor cell-based vaccine has been found to significantly extend the time to relapse from 0.6 years to 1.6 years [4]. Furthermore, survival rates at 3-year followup increased from 33 percent to 53 percent. Several large randomized phase III trials are under way, and reports on the findings from all of these studies can be expected in 2004 and 2005. The second principle for producing vaccine for malignant melanoma involves using short peptides from melanoma-associated antigens. Vaccination with these peptides has resulted in the regression of cancer. However, large clinical trials have not been conducted.

As with melanoma, tumor cell-based vaccines and vaccines based on specific antigens have been used in treating colon cancer. A randomized phase III trial from the Netherlands included 254 patients with colon cancer at stages II (n=170) and III (n=84)[9]. The patients were vaccinated with cells taken from their own tumors and BCG (Bacillus Calmette-Guérin) as adjuvant treatment. After 5 years of followup (median value), 20 percent of the vaccinated patients had relapsed compared to 32 percent in the control group (p=0.02). The greatest benefit was observed at stage II where only 11.8 percent relapsed versus 27.1 percent in the control group. The estimated relapse rate had been reduced by 56 percent (p=0.01). The relapse risk at stage III in the group that received vaccine was 35 percent versus 41 percent in the control group, ie, an estimated reduction in relapse risk of 12 percent (p=0.09). There was also a tendency toward improved total disease-specific survival at stage II (p=0.09). This vaccine is known as Onco-Vax and has been tested in expanded phase III trials for possible approval from the U.S. Food and Drug Administration (FDA). The disadvantages of such vaccines are that they are complicated to produce and are individual-specific. Furthermore, in only about 60 percent of the cases can vaccines be successfully produced from patients' tumors.

Clinical trials involving the use of specific antigens are now under way. More comprehensive trials have been conducted with tumor antigens CEA and EpCAM. However, it is too early to judge their clinical effects. In a preliminary pilot study, somewhat over 40 patients with metastasized colon cancer were vaccinated when standard treatment was no longer judged to be effective. The median survival was 18 months in patients whose immune systems responded positively to treatment, compared to 9 months in patients who did not respond to this treatment [10]. These results, among others, provide the basis for an ongoing prospective randomized phase III trial of metastasized colon cancer that combines chemotherapy and vaccination. Results from this study are expected in 2007.

In breast cancer, a vaccine is being tested against the oncoprotein, HER2/neu. This is the same antigen at which the antibody agent Herceptin is targeted (see Alert Report Trastuzumab (Herceptin®) for metastasized breast cancer. Clinical results are not yet available.

Several early vaccination attempts for pancreatic cancer are under way using various cancer antigens, eg, RAS, telomerase, MUC-1, and p53. Also, a phase III trial has been initiated in Europe for non-surgically treatable pancreatic cancer where a comparison involves adding gastrin vaccination to gemcitabine treatment.

Very early clinical trials for ovarian cancer are under way involving vaccination with HER2/neu (see above) and MUC-1.

Prophylactic and therapeutic early clinical trials in cervical cancer are under way using vaccine based on human papillomavirus, type 16, which is one of the HPV vira associated with this disease. In a prospective randomized trial, prophylactic vaccination reduced the incidence of persistent HPV-16 infection and cervical intraepithelial neoplasia (tumor formation) from 3.8 per 100 women-years in the risk for infection in the control group to 0 in the vaccination group [5].

Extensive prophylactic vaccination trials using hepatitis B vaccine in liver cancer are under way in East Asia. A reduction in the incidence for liver cancer has already been reported in clinical epidemiology trials.

Cancer vaccines have not yet been approved for use in Sweden, and this will probably take another 5 to 10 years. Comprehensive phase III trials are under way in melanoma, non-Hodgkin's lymphoma, colon cancer, and multiple myeloma. Judgements on the clinical effectiveness of these vaccines cannot be rendered before these trials are complete. Current phase III trials are targeted at adjuvant treatment. The treatment results that formed the basis for the ongoing phase III trials are encouraging. Experience gained to date from therapeutic vaccines suggests that quality of life related to this type of therapy is good.

Risks and side effects

Since all cancer vaccines are composed of antigens that are also found in normal cells, there is a risk that vaccinated individuals may experience autoimmune side effects. To date, several thousands of patients have been vaccinated in various studies without observed side effects, with the exception of vitiligo (white, pigment-poor patches on the skin) in melanoma. Other reported side effects include local inflammatory reactions. The risks for autoimmune phenomena increase with the use of more powerful cancer vaccines.

Costs and cost effectiveness

Initially, vaccine prices are found to be relatively high and vary widely depending on the production process used. The costs to produce vaccines remain uncertain, but are estimated to be 50 000 SEK for individual vaccines and 25 000 SEK per patient for general vaccines. Assuming that 7 or 8 outpatient visits related to vaccination would be required at a cost of 2 000 SEK per visit, the total treatment cost, including immunostimulants, is estimated to range between 65 000 SEK and 100 000 SEK.

The costs for prophylactic vaccination cannot be estimated from data currently available.

Structure and organization of health services

Therapeutic cancer vaccines will have little effect on the use of established methods since they will be administered as a complement to these methods. Therapeutic cancer vaccination will take place within the framework of current cancer services and will not require special resources to any great extent. The production of cancer vaccines may, however, place greater resource demands on the laboratories that produce these vaccines, particularly if the trend is toward producing patient-specific vaccines.

Currently, it is difficult to predict how prophylactic vaccines will impact on the structure and organization of health services.

Ethical aspects

There are no ethical consequences associated with cancer vaccination, except for the risk of developing autoimmune phenomena in patients who have already been cured by primary treatment. However, this risk is judged to be small given that such phenomena have not been observed after treatment in large numbers of patients.

Diffusion and current evaluation research

Cancer vaccination remains an experimental method and is currently used only in a research context. To date, approximately 100 patients have been vaccinated in Sweden at the Karolinska Hospital and the university hospitals in Lund and Linköping. Current studies focus on colon cancer, breast cancer, cervical cancer, malignant melanoma, multiple myeloma, chronic lymphatic leukemia, and glioma. These are phase I and phase II trials. Outside of Sweden, major studies are under way in Germany, Belgium, Holland, France, England, Italy, Australia, the United States, and Canada.

Expert

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