EJC SUPPLEMENTS 5 (2007) 29–32

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Vaccines: A rapidly evolving technology – Are the hurdles being addressed?

L. Håkansson[a,*], *A. Dalgleish*[b], *K.J. Kallen*[c], *M. Schuessler-Lenz*[d]

[a]*Division of Clinical Tumour Immunology, Department of Oncology, University Hospital of Linköping, SE-581 85 Linköping, Sweden*
[b]*St. George's Hospital, University of London, Blackshaw Road, London SW17 0QT, United Kingdom*
[c]*Global Clinical Development Unit – Oncology, Merck-Serono KGaA, Frankfurterstrasse 250, 64293 Darmstadt, Germany*
[d]*Division Medical Biotechnology, Paul-Ehrlich Institute, Paul-Ehrlich-Strasse 51-59, D-63225 Langen, Germany*

ARTICLE INFO

Keywords:
Therapeutic/prophylactic cancer vaccines
Escape mechanisms
Enhancing therapeutic efficacy

ABSTRACT

Vaccination usually works in infectious disease, why not in Cancer? Differences in the potency of microbial and cancer antigens, poor initiation of an immune response due to inadequate expression of tumour associated antigens, weak antigens or tolerance induction and local immune suppression were considered. There is a big difference between a therapeutic and a prophylactic vaccine.

The opinion of the expert group was that an improved therapeutic efficacy can hardly be expected by further variation of types of vaccines, schedules, routes of administration and adjuvants alone. A major hurdle for developing therapeutic cancer vaccines is the need to effectively monitor the immune response and to be able to use this in an adaptive trial approach.

End-points of assessment should be different from standard treatments as complete response or partial responses are usually low, unless combined with other therapies.

In order to focus resources to overcome the hurdles of enhancing the therapeutic efficacy of cancer vaccines the Cancer Vaccine Clinical Trial Working Group, representing academia and the pharmaceutical and biotechnology industries has in a consensus process defined 'A clinical development paradigm for cancer vaccines and related biologics'.

1. Introduction

This session was an in-depth analysis to explore the reasons why vaccines against cancer have not been developed to the point where clear clinical benefit has been demonstrated.

Several reasons for this have been discussed: Poor initiation of an immune response due to inadequate expression of tumour-associated antigens, weak antigens or tolerance induction. Problems specific to vaccinating against cancer antigens that were discussed included the concept of non-immunogenic tumours and whether such exist when the vaccine is combined with the right adjuvant. The fact that weak tumour-associated antigens could possibly make better vaccines than strong antigens (whose T-cell repertoire would more likely have been deleted/tolerated) has to be considered. The concept of tolerance and local immune suppression were considered and the real practical problem of a local secretion of immunosuppressant cytokines, such as IL-10 and TGF-β, and other tumour-derived substances interfering with even an ineffective immune response was discussed with the conclusion that the knowledge about these suppressor mechanisms are still not sufficient to allow therapeutic measures to overcome them.

* Corresponding author.
E-mail address: leif.hakansson@lio.se (L. Håkansson).
1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2007.09.004

Other possibilities included the expression of certain molecules, such as DAF CD55 in order to protect tumours from complement-dependent cytotoxicity or apoptosis inhibitors such as BCL2 to block immune-mediated tumour cell death.[1,2]

Vaccination usually works in infectious disease, why not in Cancer? Differences in the potency of microbial and cancer antigens and cancer-related immunosuppression seems to be of importance in this context. It is worth noting that where cancer is clearly associated with infection, the prophylactic cancer vaccines can be very effective with regards to incidence. The first of these is liver cancer (hepatoma) caused by HBV, a vaccine which has been available for over 20 years and which by preventing infection in the first place will have an 80–90% predicted reduction in incidence.[3] The recent success of two anti-HPV vaccines from Sanofi Aventis and GSK could have the same dramatic effect on reducing the incidence of cancer of the cervix in the next few years.[4] In this regard, it is worth noting that not all infections that cause cancer can be readily vaccinated against and it is anticipated that a vaccine against hepatitis C virus, which also causes liver cancer after decades of chronic infection, will be much more difficult to develop.

2. Vaccines in cancer today

With regards to vaccines against cancer, it is appreciated that there is a big difference between a therapeutic vaccine with macroscopic residual disease as opposed to a prophylactic vaccine given after total surgical resection to reduce the chances of disease recurrence. Issues discussed with regards to both were: the type of vaccine, schedule and adjuvants. The opinion of the expert group was that various types of vaccines, schedules, routes of administration and adjuvants have been thoroughly explored and that a major breakthrough regarding the therapeutic efficacy of vaccination in cancer can hardly be expected by further variation of these parameters.

A major hurdle for developing therapeutic cancer vaccines is the monitoring of the immune response; what is the relevant immune response and how is it best measured? Initiation of an immune response can be measured as the appearance of antigen-specific T-cells in the circulation or the appearance of tumour-specific antibodies. The role of inflammatory cells being recruited to the tumour and possible cytotoxic activity are well recognised. The need to be able to monitor immune-mediated tumour regressive changes is clearly an important end-point for therapeutic vaccines.[5] The possible role of imaging methods were discussed. Nanoparticle loaded leukocytes combined with MRI are useful in the study of distribution and tumour recruitment of these cells.[6] One possibility is to use the effect on circulating tumour cells as a substitute for anti-tumour efficacy, as shown in a recent breast carcinoma study.[7] However, again the utility of such tests are limited by not measuring some important aspects of immune-mediated cancer control, e.g. recruitment of inflammatory cells and their intra-tumoural migration.

A major aspect, which was addressed, was 'is it really feasible to expect a vaccine monotherapy to be effective in a therapeutic scenario?' It is clearly accepted that monoclonal antibodies, such as Herceptin and Avastin, are more effective when given with chemotherapy and in a vaccine situation that GVAX may induce better responses when given with anti-CTLA4.[8] Therefore, there could be a compelling reason to combine biologicals early on, but this raises major regulatory hurdles with regards to combinations in early disease. The possible synergy of combinations of two non-approved biologicals raises the question of being able to obtain a licence for the combination, as opposed to having to take them through to registration individually. Also, there is now considerable literature that combining vaccines with radiotherapy, some chemotherapy regimens, and endocrine treatment can lead to better clinical outcome and that combining cytokines, anti-angiogenics and anti-inflammatory can lead to enhancement in preclinical models.[9] It is possible that not all combinations are additive or synergistic, such as TKIs, which may have a detrimental effect on immunologically active cells.

The session focused on major practical issues as to which is the best type of disease to target, the best stage and the most appropriate antigen adjuvant combination. The more recent data discussed above led to discussions as to exploring combinations from day one, where pre-clinical data was strongly supportive.

A particular practical point is, if a vaccine looks to be the best candidate but requires an adjuvant or cytokine to optimise immunogenicity, how is this best handled if both vaccine and adjuvants are in different IP ownership.

The rapid evolvement of these types of biotherapies was highlighted by an analysis of the increase of registration applications to the regulatory authorities over the years. Practical issues of the type of vaccine to be employed in a specific situation were explored in detail with specific relationship to the regulatory and other requirements, e.g. the regulatory requirements for peptide vaccines are considerably different from cell-based vaccines or genetically modified cell-based vaccine. Cell-based vaccines, if not genetically modified, are defined as somatic cell therapies. This entity and the gene therapy products are classified as advanced therapy medicinal products according to Directive 2001/83/EC annex I part IV. In this regard, the number of gene therapy clinical trial applications in the EU has increased significantly over the last 3 years from 9 in 2005, to 16 in 2006, to 23 in March 2007, with the majority of these being for cancer. A similar situation is seen for somatic cell therapy clinical trial applications, going from 13 in 2005, to 40 in April 2006 and 71 in March 2007. Again, the majority of these are in cancer. Of interest is that in the cell therapy clinical trial applications there is an increase in cancer vaccines in combination with other therapies in phase IIb and phase III trials compared to phase II studies.

With regards to assessing the effect of cancer vaccines per se, it was widely felt that the end-points of assessment are different from standard treatments in that complete response or partial responses are usually low, unless combined with other therapies. Static disease and increased quality of life has been an acceptable end-point for much of the phase II development. Indeed, a major potential benefit for cancer vaccines may be to enhance static disease in cases where there is minimal tumour burden and when disease progression is seen, for other modalities to be added. A good example of this is prostate cancer where vaccines have been shown to be effective on the relevant surrogate markers, such as PSA, and that even a reduction in rate of the rise of PSA may correlate with an increased time to disease progression. The fact

that clinical outcome is better in patients who receive the vaccine before standard endocrine treatment strongly argues for such treatments to be used before endocrine therapy.[10]

It was also highlighted that in the case of cancer vaccines, in particular, the ability to identify the predicted immune responses and to be able to analyse surrogate tumour markers for response were particularly necessary to rapidly advance suitable candidates and possible combinations into the clinic.[11]

In spite of the vast majority of cancer vaccine development work being done in melanoma, it was recognised that the vaccine with the most likely chance of immediate registration was in fact aimed at prostate cancer. This is a dendritic cell-based candidate from Dendreon, who have analysed trials to show that there is a significant survival advantage in patients given the vaccine.[12] The session agreed that clinical results obtained recently with therapeutic cancer vaccines/immunotherapies looked more promising than in the past and that a breakthrough in terms of approval for such therapies could be expected in the coming years. In fact, it would more likely be approved for non-melanoma vaccine indications, such as prostate, colorectal, lung or renal cancer.[13]

In order to focus resources to overcome the hurdles of enhancing the therapeutic efficacy of cancer vaccines the Cancer Vaccine Clinical Trial Working Group, representing academia and the pharmaceutical and biotechnology industries has in a consensus process defined 'A clinical development paradigm for cancer vaccines and related biologics'. This work was summarised at the present symposium by Hoos.[11] The rationale for this new paradigm is that cancer vaccines are different from cytotoxic drugs and other types of molecular targeted therapies and they should be developed according to more flexible and focused guidelines. Four major topics were addressed: (1) end-points for clinical trials, (2) trial designs and statistical methods, (3) technical and developmental challenges, and (4) combination therapy.

The proposed paradigm suggests therapeutic cancer vaccines to be developed in two types of clinical studies: proof-of-principle trials and efficacy trials. Proof-of-principle trials, which introduce a novel cancer vaccine into humans, should include a minimum of 20 or more patients in a homogenous, well-defined population in an adjuvant setting or without rapidly progressive disease in a metastatic setting to allow vaccines adequate time to induce biological activity and should incorporate immune and molecular markers. Objectives should include initiation of a safety database, determination of dose and schedule, and demonstration of biological activity as proof-of-principle. Biological activity is defined as any effect of the vaccine on the target disease or host immune system using biological markers as study end-points, for example, clinical, molecular, or immune response. Immune response is demonstrated if determined in two separate, established and reproducible assays at two consecutive follow-up time points after the baseline assessment. If proof-of-principle trials show such immune response, or other biological or clinical activity, efficacy trials may be initiated. If none of these end-points is met, the clinical development plan should be re-evaluated to decide if further development is warranted.[13,14]

Efficacy trials formally establish clinical benefits either directly or through a surrogate and are encouraged to be randomised studies. This is in contrast to single-arm phase II trials used for cytotoxic agents, which often use tumour response rate as the primary end-point and historical controls as a comparator. Efficacy trials may use prospectively planned adaptive designs to expand from randomised phase II into phase III studies if well-defined trigger-point criteria are met, but the cost of incorporating such design elements should be carefully evaluated. Efficacy trials can also be exploratory randomised phase II trials or conventional phase III trials. In addition, conventional clinical end-points can be adjusted to account for biological features of cancer vaccines. The concept of efficacy trials allows for an early assessment of vaccine efficacy based on credible prospective data.

3. Summary

Delayed benefit (response) occurs after disease progression. Therefore, the paradigm calls for continuing vaccination therapy if (1) progression is not rapid and is clinically insignificant; (2) no other therapy is immediately required; or (3) no effective therapy is available. Often vaccinated patients will show no clinical response other than stable disease but a progression will show marked clinical responses to other modalities, such as radiotherapy or chemotherapy. Hence, vaccines which do not induce a CR on PR can greatly increase survival with classical treatments and may explain the unexpected Dendreon results.

Conflict of interest statement

The four authors of this paper can confirm that there is no conflict of interest involved in this paper, nor in their participation in this entire event.

REFERENCES

1. Dalgleish A. Overcoming technical challenges in the development of cancer vaccines. *IDrugs* 2007;**10**(7):463–7.
2. Dalgleish AG, Whelan MA. Cancer vaccines as a therapeutic modality: the long trek. *Cancer Immunol Immunother*.
3. Yu SZ. Primary prevention of hepatocellular carcinoma. *J Gastroenterol Hepatol* 1995;**10**(6):674–82.
4. Chan JK, Berek JS. Impact of the human papilloma vaccine on cervical cancer. *J Clin Oncol* 2007;**25**(20):2975–82.
5. Ward S, Dalgleish A. Therapeutic cancer vaccines. *Vaccine* 2007;**25**(Suppl. 2):B1–3.
6. Huh YM et al. In vivo magnetic resonance detection of cancer by using multifunctional magnetic nanocrystals. *J Am Chem Soc* 2005;**127**(35):12387–91.
7. Dawood S, Cristofanilli M. Integrating circulating tumor cell assays into the management of breast cancer. *Curr Treat Options Oncol* 2007;**8**(1):89–95.
8. Hodi FS, Dranoff G. Combinatorial cancer immunotherapy. *Adv Immunol* 2006;**90**:341–68.
9. Schlom J, Arlen PM, Gulley JL. Cancer vaccines: moving beyond current paradigms. *Clin Cancer Res* 2007;**13**(13):3776–82.
10. Arlen PM et al. Antiandrogen, vaccine and combination therapy in patients with nonmetastatic hormone refractory prostate cancer. *J Urol* 2005;**174**(2):539–46.

11. Hoos A et al. A clinical development paradigm for cancer vaccines and related biologics. *J Immunother (1997)* 2007;**30**(1):1–15.
12. Dendreon. Dendreon's vaccine failed to obtain marketing approval from the FDA in the aftermath of the meeting despite a positive ODAC votum. FDA.gov/Dendrion; 2007.
13. Dalgleish A, Pandha H. Tumor antigens as surrogate markers and targets for therapy and vaccines. *Adv Cancer Res* 2007;**96**:175–90.
14. Copier J, Whelan M, Dalgleish A. Biomarkers for the development of cancer vaccines: current status. *Mol Diagn Ther* 2006;**10**(6):337–43.