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Non-clinical development of cancer vaccines: Regulatory considerations

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Abstract

This paper discusses regulatory requirements essential during the non-clinical development of cancer vaccines. DNA vaccines and vaccines containing monoclonal antibodies are specifically addressed. ICH, CHMP, FDA, and WHO guidance documents in addition to scientific literature are reviewed and the regulatory framework, including respective EMEA and the FDA divisions responsible for review and assessment of cancer vaccines, is described. Selection criteria for an appropriate animal model for efficacy and/or toxicity studies are discussed.

Keywords: Toxicology; Animal model; Regulatory affairs; Biotechnology; Tumour; Anti-idiotypic; DNA vaccines; Monoclonal antibodies; EMEA; FDA

1. Introduction

Cancer Vaccines (CaVs) fight cancer by stimulating the immune system and turning it against cancer cells. This concept is highly topical and rapidly evolving, both from the regulatory and the scientific viewpoint, driven by a growing business interest. CaVs are particularly challenging since the variety of scientific approaches used in the development of CaVs is vast, ranging from non-specific immunostimulants to autologous tumour cell lysates or highly specific DNA vaccines (for review see Hipp et al., 2000; for reviews see Mocellin et al., 2004; Moingeon, 2001; Pardoll, 1998).

Potential CaV candidates are in advanced clinical trials; one CaV (being an autologous tumour cell lysate vaccine, developed by Liponova, Germany) is currently being assessed by the EMEA. However, to date no cancer vaccine has been approved for human use by the EMEA or the FDA and so far no guidance is available that specifically covers the whole range of different CaVs. This paper reviews current ICH, CHMP, FDA, and WHO guidance documents in addition to scientific literature and discusses requirements essential during their non-clinical development. Specific issues concerning the use of animal models are addressed as well as additional hurdles resulting from the use of (new) adjuvants.

1.1. Mechanism of action

Active immunotherapy strategies may elicit non-specific or specific anti-tumour reactions by stimulating the patient's immune system.

Non-specific immunostimulants aim to reverse immunosuppression induced by the tumour. Boosting the activity levels of the immune system is expected to result in the rejection of cancer tissue. This kind of product is usually administered in adjuvanted form to enhance the immune response against the cancer cells induced by the vaccination antigen, but in some cases the adjuvant may be administered as main therapy itself.

Specific CaVs induce a tumour-specific immune response by immunizing patients with tumour cells or their antigenic components, so called Tumour Associated

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Antigens (TAAs)[1] These are antigens, which are either mutated or selectively or abundantly expressed in malignant, but not in normal cells. Specific recognition of TAA is provoked to elicit a persistent immune memory. The cellular basis of the anti-tumour immune memory involves generation and extended persistence of expanded populations of T- and B-lymphocytes that specifically recognize a specific TAA and eliminate tumour cells (Bocchia et al., 2000).

It has been observed that tumours can escape single-antigen or single-epitope vaccines if the tumour fails to express (or expresses only weakly) the particular antigen targeted by the CaV. To overcome immunological evasion, multivalent or multi-epitope vaccines are being developed, containing multiple, defined TAAs, combining several antigens in a single formulation. Another approach is to employ whole inactivated cancer cells containing the entire spectrum of TAAs in an ultravalent formulation (for reviews see for example Mocellin et al., 2004; Pardoll, 1998).

CaVs are intended both, for preventive or therapeutic clinical application. In contrast to therapeutic vaccines, the use of preventive CaVs is based on an immune system that is neither impaired by tumour- or treatment-induced suppression. In addition, the immune system is moreover not tolerant to TAAs that have been encountered in the absence of correct presentation and co-stimulatory/danger signals. The use of overexpressed or mutated proteins, or mutated oncogenic growth factor receptors as TAAs provides relevant targets for specific immunoprevention (Finn and Forni, 2002; Moingeon, 2001).

Although the majority of CaV products are biotechnology-derived, some are not: peptide CaVs may not fall into the definition of biologics as they are chemically synthesized and may therefore be regarded as small molecule drugs. The possible regulatory implications are addressed below.

This review focus on the requirements for DNA vaccines and vaccines containing monoclonal antibodies.

DNA vaccines use naked DNA as well as viral vectors or bacteria for immunization (Conry et al., 1999; Marshall et al., 2000; Mincheff et al., 2000; von Mehren et al., 2001). The vectors encoding for a specific TAA can enter the patient cells, where they become the in vivo DNA template for the production of the specific protein antigen (Hipp et al., 2000). Vaccination induces strong and long lasting immune responses against the expressed antigen (and the virus in the case of viral vector products), involving both the humoral and cellular arms of the immune system (Hipp et al., 2000; Kim et al., 2001).

Anti-idiotypic antibodies can potentially induce a human anti-anti-idiotypic response. The anti-anti-idiotypic antibodies mimic the original antigen (Perelson, 1989). Because of this mimicry, the anti-idiotype molecule can be used as a surrogate vaccine in place of natural tumour-associated antigens by stimulation of cellular or humoral immune responses. This vaccination strategy requires only small amounts of vaccine preparation and permits vaccination against non-protein antigens that are difficult to clone (e.g., carbohydrates) (Mocellin et al., 2004).

2. EU and US regulatory environment

The EU Directive 2004/27/EC (amending Directive 2001/83/EC) classifies CaVs as "active substances for which the therapeutic indication is the treatment of cancer"; CaVs are therefore subject to the centralised procedure (EC, 2004). The centralized procedure is moreover mandatory for biotechnology products, which includes the majority of CaVs. National Authorities may be involved in product development only within the framework of scientific advice procedures.

FDA's regulation of CaVs is not uniform and depends upon the nature of the individual vaccine. Overlapping competences may require early agency contact to define the responsible office for each new product. Anti-idiotypic CaVs, vaccines containing bispecific antibodies, or antibody fragments CaVs are regulated by CDER's Oncology Division and the Office of New Drugs VI (this Office of Drug Evaluation, ODE, was created in 2004). The Office of Biotechnology Products (within CDER's Office of Pharmaceutical Science; also created in 2004) may also be involved in the regulatory reviews. Small synthetic (i.e., non-biological) peptide based vaccines are the responsibility of ODE II.

CBER is generally responsible for vaccines (defined as "products intended to induce or increase an antigen specific immune response for prophylactic or therapeutic immunization"), regardless of the composition or method of manufacture. CBER's oncology branch is responsible for regulation of cellular and tissue based products including tumour-cell based vaccines, dendritic and DNA plasmid vaccines. Two groups in CBER may therefore review and assess CaVs, the Office of Vaccines Research and Review and the Office of Cellular, Tissue and Gene Therapies, in the case of viral vectors, gene or cellular therapy.

2.1. Regulatory guidance documents

Varied approaches are employed by companies to develop CaVs and this variability creates an enormous challenge for the regulatory agencies when discussing individual programs, and considering the required non-clinical studies. Accordingly, ICH S6, the harmonized guidance providing recommendations on the preclinical development of biotechnology products in general states: "All regions [European Union,

[1] *Abbreviations used:* APC, antigen presenting cell; CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; CHMP, Committee for Medicinal Products for Human Use; CPMP, Committee for Proprietary Medicinal Products; DIC, disseminated intravascular coagulation; EMEA, European Medicines Agency; FDA, Food and Drug Administration; FAb, fragment antigen binding; HLA, human leukocyte antigen; ICH, International Conference on Harmonisation; MTD, maximum tolerated dose; ODE, Office of Drug Evaluation; PCR, polymerase chain reaction; PD, pharmacodynamics; PK, pharmacokinetics; SCID, severe combined immunodeficiency; TAA, tumour associated antigen; WHO, World Health Organization.