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Review

Design of clinical trials for therapeutic cancer vaccines development

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ABSTRACT

Advances in molecular and cellular biology as well as biotechnology led to definition of a group of drugs referred to as medicinal products of advanced technologies. It includes gene therapy products, somatic cell therapeutics and tissue engineering. Therapeutic cancer vaccines including whole cell tumor cells vaccines or gene modified whole cells belong to somatic therapeutics and/or gene therapy products category. The drug development is a multistep complex process. It comprises of two phases: preclinical and clinical. Guidelines on preclinical testing of cell based immunotherapy medicinal products have been defined by regulatory agencies and are available. However, clinical testing of therapeutic cancer vaccines is still under debate. It presents a serious problem since recently clinical efficacy of the number of cancer vaccines has been demonstrated that focused a lot of public attention. In general clinical testing in the current form is very expensive, time consuming and poorly designed what may lead to overlooking of products clinically beneficial for patients. Accordingly regulatory authorities and researches including Cancer Vaccine Clinical Trial Working Group proposed three regulatory solutions to facilitate clinical development of cancer vaccines: cost-recovery program, conditional marketing authorization, and a new development paradigm. Paradigm includes a model in which cancer vaccines are investigated in two types of clinical trials: proof-of-principle and efficacy. The proof-of-principle trial objectives are: safety; dose selection and schedule of vaccination; and demonstration of proof-of-principle. Efficacy trials are randomized clinical trials with objectives of demonstrating clinical benefit either directly or through a surrogate. The clinical end points are still under debate.

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1. Introduction

The drug development is a multistep complex process. It is usually divided into two major phases — preclinical and clinical. The preclinical development comprises of (i) pharmacology, (ii) toxicology, (iii) pharmacokinetics and (iv) chemistry and pharmacy of the drug. Pharmacological analyses include (i) *in vitro* activity, (ii) *in vivo* activity, (iii) activity on isolated organs, and (iv) initial proofs of tolerability. Toxicological studies include (i) acute toxicity (Lethal Dose — LD50 and Maximal Tolerated Dose — MTD), (ii) subacute toxicity, (iii) mutagenicity, (iv) embryotoxicity, (v) reproduction toxicity, (vi) chronic toxicity, and (vii) carcinogenesis. Pharmacokinetics of the drug comprise of (i) absorption, (ii) distribution, (iii) metabolism, (iv) elimination and (v) selection of best animal species (for chronic toxicology studies). Finally, chemistry and pharmacy include (i) formulations, (ii) administration routes, (iii) stability, (iv) selection of excipients, and (iv) controlled release of the drug.

The clinical development is divided into four phases: I, II, III (A and B) and IV. Phase I is usually performed in healthy volunteers, however in oncology it is performed on terminal patients. The aim of the phase I study is a proof-of-concept, determination of the metabolism and pharmacologic actions of drugs in humans, dose escalation, safety to gather information on adverse events and tolerability (Maximal Tolerated Dose). The number of patients in the study varies between 20 and 80, however, the minimal size is 9. Phase II is performed in patients and is useful in obtaining information on doses and efficacy (clinical and laboratory), short time side effects (size: 100–300; usually 40 patients). Phase III is also performed in patients and should provide information on efficacy (benefit–risk relationship) and tolerability (versus comparators), — size: 1000–3000; however, about 360 may be indicative. The phase IV is performed in patients, at the approved dose, in the approved way of administration, in the approved indication(s) and in the normal use of the drug. The aim of this study phase is to obtain further information about safety (late toxicity) in a much larger patients' population (benefit/risk ratio). Size of these trials is between 4000 and 12,000 patients (Fig. 1).

Delineated above drug development process is a continuous task which is strictly monitored by regulatory authorities. Any changes or modifications to it need negotiations with authorities and an approval. Current legislation and strict monitoring by authorities provide safety for patients participating in clinical trials of new drugs. Patients' benefit/risk ratio is clearly defined and should be superior to the benefit of the drug provider. In the same time due to the technological development and expectations of the society philosophy of cancer therapy is continuously changing. Highly toxic chemical therapies are being replaced by nontoxic biological treatment modalities. Moreover, it is generally accepted today that there is no cancer drug which displays 100% efficacy but may rather bring benefit to the fraction of patients. Accordingly, a new philosophy of treatment so called personalized oncology has been created.

Recently a new category of medicinal products of advanced technologies was defined (Regulation, 2007/1394/EC). It includes medicinal products of gene therapy, medicinal products of somatic cells therapy, and products of tissue engineering. Medicinal products of gene therapy may be based on allogeneic and xenogeneic cells, autologous cells or vectors caring therapeutic genes. They comprise naked nucleic acids, nucleic acids or non-viral vectors, viral vectors and genetically modified cells. In turn, medicinal products of somatic cell therapy include, cells

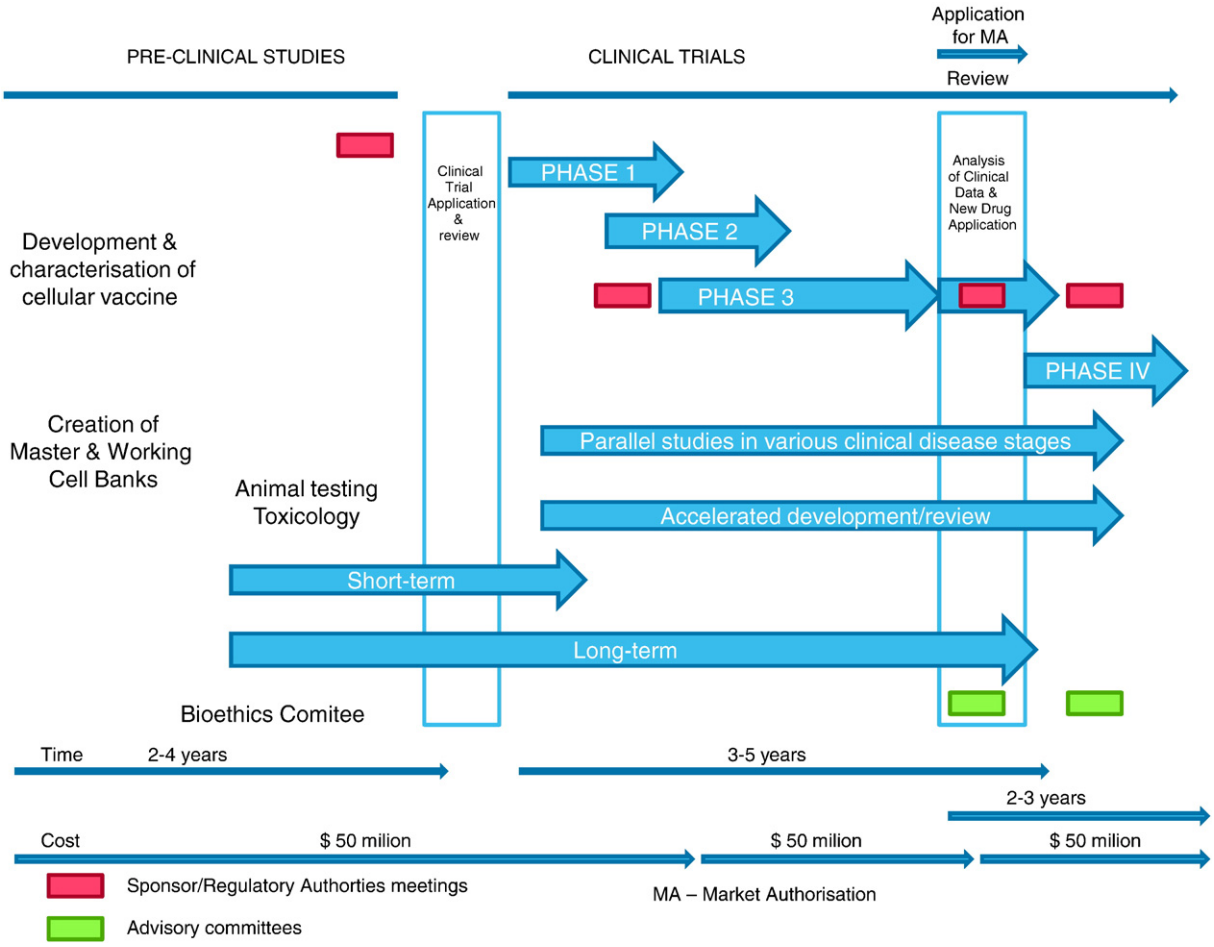

Fig. 1. Drug development process.