Phase I study: determining toxicity and immunity of the p53 synthetic long peptides vaccine combined with Interferon-alfa in patients treated for colorectal cancer

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON33981

Source
ToetsingOnline

Brief title
p53-SLP vaccine in combination with IFNα

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Colorectal cancer, large bowel and rectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ISA pharmaceuticals

Intervention

Keyword: colorectal cancer, long peptides, p53, vaccination

Outcome measures

Primary outcome

Safety will be assessed during the whole study by collecting all adverse events according CTC version 3.0 (with a focus on administration site reactions), vital signs, blood-chemistry and haematological parameters. Immunogenicity will be assessed by an array of complementary immunological assays which focus on p53-specific T-cell proliferation, enumeration of circulating IFNγ-producing T-cells, Th1/Th2 cytokine production, and p53 protein recognition by circulating and vaccine-site-homing T-cells. However, the primary endpoint is determined by the directly ex-vivo detectable p53-specific CD4+ T-cell response and is defined by the percentage of CD3+CD4+ T cells that up-regulate the activation markers CD154 and CD137 upon stimulation with p53 antigen in freshly tested PBMC as measured by multiparameter flowcytometry. The immunological endpoint is successful if a combination of the p53-SLP vaccine combined with subcutaneous injection of IFN* is capable of inducing a directly ex-vivo detectable p53-specific CD4+ T-cell response in at least 70% of the vaccinated patients.

Secondary outcome

The secondary endpoint is successful if a combination of the p53-SLP vaccine

combined with subcutaneous injection of interferon-alfa is capable of inducing a more pronounced Th1 response in the vaccinated patients. Th1 response is defined as the number of IFNγ producing T-cells in ELISPOT, the proportion of IFNγ producing cells in the total population of p53-specific T-cells measured by multiparameter flow cytometry, as well as the amount of IFNγ in the supernatant of proliferation assays. All which were low in our previous trial.

Study description

Background summary

Colorectal cancer is the second most frequent cancer in the Netherlands. Despite treatment 45% of all colorectal cancer patients die within 5 years. Efforts to improve survival in patients with advanced colorectal cancer have had only limited success. P53, is due to a mutation a frequently over-expressed protein in colorectal cancer patients. This over-expression provides an immunological window for immunotherapy of colorectal cancer. In a recent phase I study we showed that vaccination with p53 synthetic long peptides (p53-SLP) is capable to induce a systemic p53 specific T-cell response in the majority of patients. Despite the induction of p53-specific T-cell immunity in vaccinated patients, the p53-specific T helper responses are probably too weak to become truly effective as they were not associated with a good Th1 polarization. Most likely this is due to the fact that the p53-SLP vaccine did not contain a compound to activate dendritic cells (DC). DC-activating agents, including Interferon-alfa (IFNα), are known for their capacity to strongly enhance Th1-associated T-cell responses.

Study objective

Primary objectives of the study are to assess whether the administration of p53-SLP together with the local administration of IFNα is safe and able to induce a strong (directly ex-vivo detectable) p53-specific CD4+ T-cell response.

Secondary objective is to assess whether the administration of p53-SLP together with the local administration of IFNα is able to induce an overall significantly stronger p53-specific Th1 response than observed in the group of patients vaccinated in our previous trial.

Study design

Exploratory phase I trial

Intervention

Eligible patients will receive 2 vaccinations consisting of 9 synthetic long peptides, 300 µg per peptide, emulsified in DMSO / 20 mM PBS / Montanide ISA 51 20/30/50 v/v/v by subcutaneous injection in one of the arms. Vaccinations will be given with a three week interval. Pegylated IFNα (Pegintron, Schering-Plough) will be injected in close proximity of the vaccination site one hour afterwards.

Study burden and risks

Patient will visit the clinic during the trial five times more compared to routine follow up in a period of four months. During the visits, patients are two times vaccinated in combination with application of the adjuvant, blood is drawn (2 times 215 mL, 3 times 15 mL), a skin biopsy from the second vaccination site is punched. Results from two previous phase I/II trial with both colorectal and ovarian cancer patients showed that the p53-SLP vaccine is safe. We expect that adverse events in this trial mainly consist of swelling and redness of the vaccination site, due to the vaccine induced immune response.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Willing and able to comply with the protocol and to provide informed consent in accordance with institutional and regulatory guidelines
- Patients must be 18 years or older.
- Histological proven colorectal carcinoma
- At least one month after last treatment
- Life expectance of more than 6 months
- Patients of child-bearing potential should test negative using a serum pregnancy test and agree to utilize effective contraception during the entire treatment and follow-up period of the study
- Patients must be ambulatory, with an WHO performance status of 0 to 1
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; conditions should be discussed with the patient before registration in the trial
- Baseline laboratory findings; haemoglobin > 6.0mmol/L, white blood cells (WBC) > 3,000 x 109/L, lymphocytes > 1,000 x 109/L, platelets > 100 x 109/L, HIV- and HBV-negative

Exclusion criteria

- History of an autoimmune disease or other systemic intercurrent disease that might affect the immunocompetence of the patient, or patients receiving immunosuppressive therapy including transplant recipients
- History of a second malignancy except curatively treated low-stage tumours with a histology that can be differentiated from colorectal cancer
- Any condition that in the opinion of the investigator could interfere with the conduct of the study
- Radiotherapy, chemotherapy or other potentially immunosuppressive therapy administered within 4 weeks prior to the enrolment visit
- Receipt of another investigational product within the previous 4 weeks or at any time during the study period
- Receipt of prior P53 directed immunotherapy

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2009
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PEGintron
Generic name:	Peginterferon-alfa-2b
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-07-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	22-01-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-004611-35-NL
CCMO	NL24089.000.08