Combination of Platinum standard first front line chemotherapy and Vaxira vaccine in patients with advanced non- small- cell lung cancer

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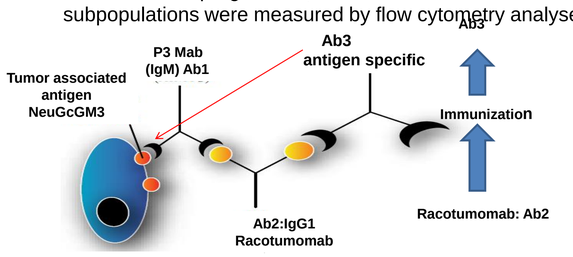
Background:

The combination of vaccines and chemotherapy holds promise for cancer therapy, but the effect of cytotoxic chemotherapy on vaccine-induced antitumor immunity is unknown.

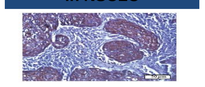
Vaxira is a therapeutic vaccine that induces an immune response against Neu- Gc containing gangliosides sulfatides and others antigens expressed in several tumors. Vaxira is composed by Racotumomab and aluminum hydroxide as adyuvant. Racotumomab is an antiidiotype murine monoclonal antibody specific to P3 Ab1 MAb, an antibody which reacts to NeuGc-containing gangliosides, sulfatides and other antigens expressed in tumors. Phase I trials conducted in patients with advanced melanoma, breast and lung cancer have demonstrated the low toxicity and high immunogenicity of Vaxira.

Methods:

An exploratory phase I study was conducted to assess the feasibility of combining Vaxira vaccine with the standard first line chemotherapy used in advanced NSCLC patients and determine the effect on Racotumomab-specific humoral immune responses. Twenty patients with histological confirmed NSCLC stages IIIB/IV were treated with cisplatin/vinblastine as standard first front line therapy according the treatment established in the Oncology Therapeutic Guidelines. Vaccination schedule consisted in the administration of 1mg of Racotumomab by intradermic route. The first 5 doses were administered every 14 days concomitantly with the first line chemotherapy and the rest every 28 days. Vaccination was not interrupted due to disease progression, and continued until death or deterioration of PS. Humoral immune responses against Racotumomab anti-idiotype and NeuGcGM3 antigen were measured by standard ELISA assays, and changes in lymphocyte cells subpopulations were measured by flow cytometry analyses (FACS).



NeuGcGM3 expression in NSCLC



Pathology Research International , 2011
BMC Cancer,2009

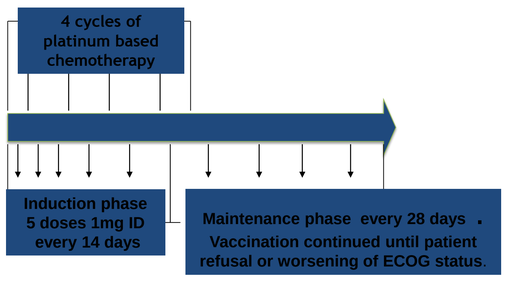
Vaxira vaccine: Racotumomab anti-idiotype Mab/ aluminum hydroxide

Patients clinical and demographic characteristics

	N=20	
	Mean (years)	Range
Age	62	40-75
	IIIb	IV
Stage	8	12
	F	M
gender	9	11

	N=20		
	< 5	5-15	+ 15
Vaccination doses	2	18	0
	RP	EE	EP
CT Response.	7	7	2
	0	1	2
PS	12	8	--

Treatment schedule



Results:

The combination of Vaxira vaccine and systemic chemotherapy has an acceptable safety profile in patients with advanced NSCLC

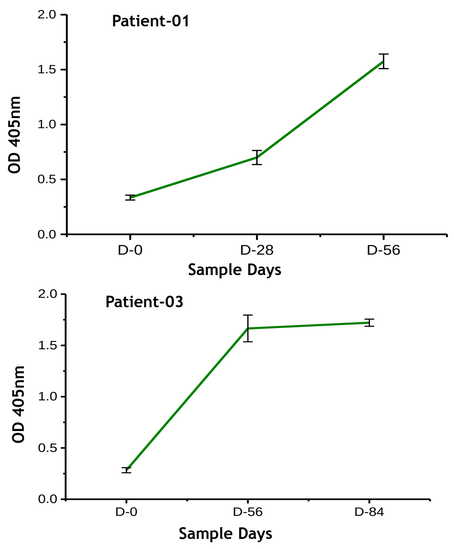
Safety: More common related Vaxira vaccine Adverse Events (AEr): Only I-II grade (CTC-NCI version (3.00)

Adverse Events	Grade CTC-NCI	Frequency	%
Injection site reaction	I-II	22	55
Nausea	I-II	4	10
Flushing	I	2	5
Vomiting	I	2	5
Skin reaction	I	1	2.5
Fever	I	4	10
Tachycardia	I	1	2.5
Bone pain	I	1	2.5
Headache	I	2	5
Fatigue	I	1	2.5
TOTAL	I-II	40	100

Vaccination of advanced NSCLC patients with Vaxira vaccine induced an 1E10 specific Ab3 response characterized by high titers.

Maximum antibodies titers and day of humoral response versus whole 1E10 mAb in patients treated with the anti-idiotype Vaxira vaccine.

Patients	1/Titer	Day
ZMP-01	12800	56
PVC-02	6400	180
AChH-03	25600	84
POI-04	12800	56
MMP-06	25600	56
TGB-07	3200	56
HMR-08	12800	56
ASC-09	25600	84
LALR-11	25600	56
TNT-12	6400	56
MAL-10	25600	56
AFS-13	12800	56
GLV-14	6400	56
OLGV-15	25600	28
JFR-18	25600	84
Mean	16853	68
Median	12800	56

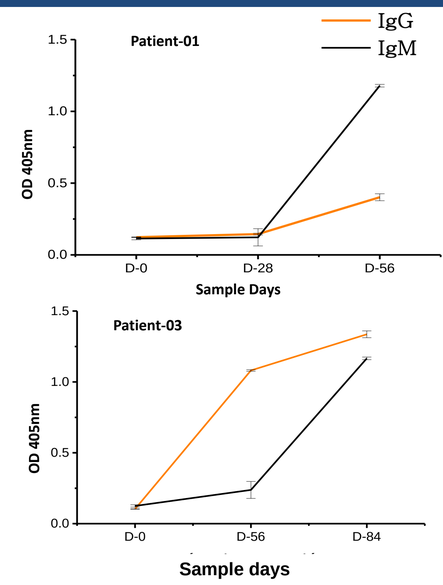


Kinetics of anti 1E10 mAb response in NSCLC patients with concomitant treatment with CT and Vaxira anti-idiotype vaccine.Sera from two representative vaccinated patients (patient ZMP-01 and AChH-03) were added to ELISA plates coated with 1E10 mAb..

Specific IgM and IgG isotypes antibody response against GM3(NeuGc) ganglioside was elicited by NSCLC patients immunized with Vaxira vaccine.

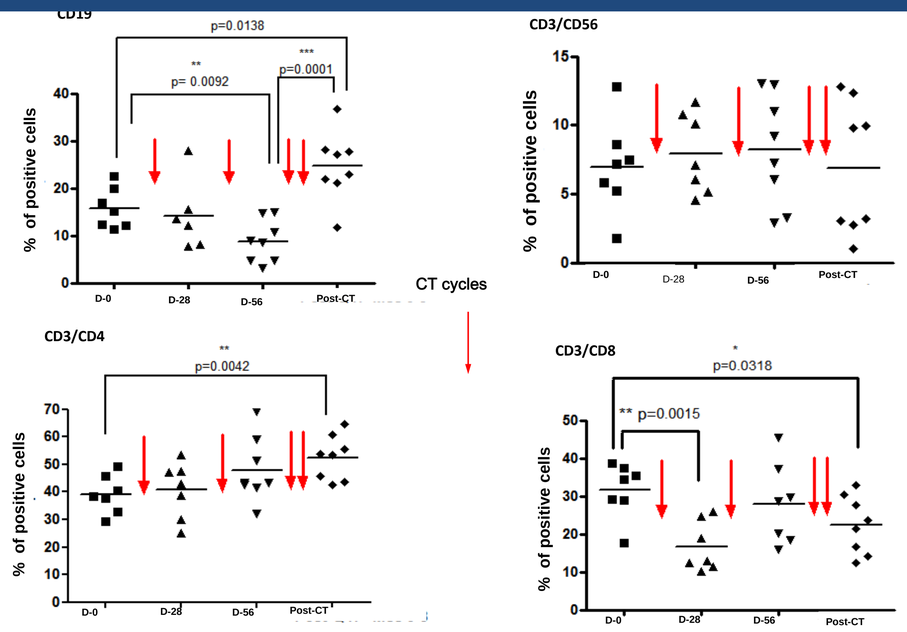
Maximum antibodies titers and day of humoral response versus ganglioside NeuGcGM3 in patients treated with anti-idiotype Vaxira vaccine.

Patients	1/IgG Titer	Day	1/IgM Titer	Day
ZMP-01	200	56	6400	56
PVC-02	200	180	400	180
AChH-03	800	84	1600	84
POI-04	0	--	200	56
MMP-06	400	56	3200	56
TGB-07	0	--	0	--
HMR-08	0	--	800	56
ASC-09	400	84	400	84
LALR-11	400	56	6400	56
TNT-12	800	56	12800	56
MAL-10	1600	56	200	56
AFS-13	400	56	800	56
GLV-14	0	---	800	84
OLGV-15	200	84	6400	84
JFR-18	6400	84	6400	84
Mean	786	56	3120	69
Median	400	56	800	56



Kinetics of antibody response versus GM3(NeuGc) ganglioside. Sera from four representative vaccinated patients (number 01 and 03) were added to ELISA plates coated with GM3(NeuGc) ganglioside. Black line represents the serological IgM response; orange line represents the serological IgM response.

The administration of CT with Vaxira vaccine made changes in lymphocyte cells subpopulations during combination treatment



Analysis of lymphocyte cells populations in Peripheral Blood Mononuclear Cells (PBMC) from patients. Red blood cells were removed from whole blood by osmotic lysis, PBMCs were washed and then staining with the corresponding antibodies labeled by FACS.

Concluding remarks

- The combination of Vaxira vaccine and systemic chemotherapy has an acceptable safety profile in patients with advanced NSCLC
- Concurrent first line standard systemic chemotherapy did not affect the generation of specific humoral responses against Mab 1E10 and NeuGcGM3 antigen following vaccination.
- The concomitant administration of the platinum based CT and the anti-idiotype Vaxira vaccine induce changes in the levels of cellular subpopulations CD19 and CD3CD8, trends to increase the CD3CD4 cells and not provoque changes in CD3CD56 cells. These preliminary data will be explore in others clinical trials
- . The present data suggest that chemotherapy does not inhibit Vaxira vaccine-mediated immune response and provide further support for evaluating novel combinations of chemotherapy and Vaxira vaccine for NSCLC and other cancers.