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WT1-mRNA dendritic cell vaccination of patients with glioblastoma multiforme, malignant pleural mesothelioma, metastatic breast cancer, and other solid tumors: type 1 T-lymphocyte responses are associated with clinical outcome

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Abstract

Cell therapies, including tumor antigen-loaded dendritic cells used as therapeutic cancer vaccines, offer treatment options for patients with malignancies. We evaluated the feasibility, safety, immunogenicity, and clinical activity of adjuvant vaccination with Wilms' tumor protein (WT1) mRNA-electroporated autologous dendritic cells (*WT1*-mRNA/DC) in a single-arm phase I/II clinical study of patients with advanced solid tumors receiving standard therapy. Disease status and immune reactivity were evaluated after 8 weeks and 6 months. *WT1*-mRNA/DC vaccination was feasible in all patients, except one. Vaccination was well tolerated without evidence of systemic toxicity. The disease control rate and overall response rate among a total of 39 evaluable patients were 74.4% and 12.8%, respectively. Median overall survival (OS) was 43.7 months among 13 patients with glioblastoma multiforme,

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41.9 months among 12 patients with metastatic breast cancer, and 48.8 months among 10 patients with malignant pleural mesothelioma, comparing favourably with historical controls reported in the literature. OS was longer in patients with stable disease at 8 weeks and disease control at 6 months versus patients without disease control at either time point. Disease control and higher OS were associated with antigen-specific type 1 $CD4^+$ and/or $CD8^+$ T-lymphocyte responses, mainly induced by *WT1*-mRNA/DC vaccination. Antigen-nonspecific type 2 $CD8^+$ T-cell responses were common before *WT1*-mRNA/DC vaccination but did not show any association with clinical outcome. Collectively, these data indicate that *WT1*-mRNA/DC vaccination is feasible, safe, and immunogenic and shows clinical activity in patients with advanced solid tumors, suggesting that it has the potential to help improve their survival.

Keywords mRNA, Wilms' tumor protein, Dendritic cell vaccination, Solid tumors, Cancer immunotherapy, Clinical trial, Type 1 T-lymphocyte response, Glioblastoma multiforme, Malignant pleural mesothelioma, Metastatic breast cancer

To the Editor,

We report on 40 patients with poor-prognosis advanced tumors who received adjuvant treatment in a single-arm phase I/II study (NCT01291420) with *WT1*-mRNA/DC, i.e. autologous dendritic cells exposed to keyhole limpet hemocyanin (KLH) and electroporated with mRNA encoding the Wilms' tumor protein (WT1) tumor-associated antigen [1, 2] (Additional File 1: Methods). *WT1*-mRNA/DC production and vaccination were feasible in 40/40 and 39/40 patients, respectively (Additional File 2: Tables S1–S6). Side effects were limited to local reactions at the injection site. The disease control and overall response rates were 64.1% and 5.1% at 8 weeks (time point T1) and 48.7% and 12.8% at 6 months (time point T2) after the initiation of *WT1*-mRNA/DC vaccination, respectively (Table 1). Median overall survival (OS) was 43.7 months in patients with glioblastoma multiforme, 41.9 months in patients with metastatic breast cancer, and 48.8 months in patients with malignant pleural mesothelioma, comparing favourably with previously reported figures of 16.0, 37.2, and 23.4 months, respectively [3–5] (Table 1; Additional File 2: Figure S1). Stable disease was observed at T1 and/or T2 in 24/39 patients (without any concomitant treatment in 12/39 patients), potentially explaining the observed benefits in terms of OS [2, 6, 7]. Achieving stable disease at T1 with disease control at T2 was associated with a longer median OS compared with failing to achieve disease control at T1 or T2 ($N = 34$, $P = 0.0356$). All patients achieving partial or complete responses also received concomitant treatment during *WT1*-mRNA/DC vaccination.

All but 1/38 patients tested (SOL36) had a delayed type hypersensitivity reaction. Most patients also exhibited type 1 T-lymphocyte responses at T1 and/or T2, comprising interferon (IFN)-γ^+ and/or tumor necrosis factor (TNF)-α^+ $CD4^+$ T-lymphocyte reactivity and IFN-γ^+ $CD8^+$ T-lymphocyte response against WT1, and TNF-α^+ $CD4^+$ T-lymphocyte reactivity against KLH (Fig. 1a). High frequencies (> 0.1%) of antigen-nonspecific interleukin (IL)-5^+ $CD8^+$ T-lymphocytes were detected in many patients at baseline (Fig. 1a), decreasing by at least 50% in 5/27 patients, increasing by at least 50% in 3/27 patients, and remaining within these bounds in 19/27 patients after *WT1*-mRNA/DC vaccination. Accordingly, most patients displayed antigen-nonspecific type 2 cytotoxic T-lymphocyte (CTL) responses at baseline, which were not consistently affected by *WT1*-mRNA/DC vaccination, whereas antigen-specific type 1 helper T-lymphocyte and CTL responses emerged *de novo* in a majority of cases after *WT1*-mRNA/DC vaccination.

High frequencies of WT1-specific tetramer$^+$ $CD8^+$ T-lymphocytes, especially those specific for the $WT1_{187-195}$ and $WT1_{235-243}$ epitopes [8], were detected in HLA-A*02:01^+ patients at baseline (Fig. 1a; Additional File 2: Figure S2). About 1/3rd of patients showed an increase post-vaccination in tetramer$^+$ $CD8^+$ T-cells specific for each of the epitopes tested, except $WT1_{126-134}$, for which half of the patients showed increased reactivity. IgG responses specific for WT1 [7] were also detected in most patients, primarily directed against the $WT1_{235-248}$ epitope, many of them already present at baseline (Additional File 2: Figure S3; Fig. 1a).

Disease control was associated with type 1 cytokine reactivity (Fig. 1b). Direct associations were detected between disease control and IFN-γ^+ and/or TNF-α^+ $CD4^+$ and/or $CD8^+$ T-lymphocyte responses specific for WT1 or KLH. IFN-γ^+ $CD4^+$ T-lymphocyte responses specific for WT1 associated directly with OS (Fig. 1b). Accordingly, antigen-specific type 1 $CD4^+$ and/or $CD8^+$ T-lymphocyte responses were associated with clinical outcome, as reported previously [9].

Additional associations were detected among immunological parameters, including IFN-γ^+ and TNF-α^+ $CD4^+$ versus $CD8^+$ WT1-specific T-lymphocyte responses, suggesting a degree of synchronicity in the overall immune response, mainly induced by *WT1*-mRNA/DC vaccination (Fig. 1b). IFN-γ^+ $CD4^+$ and $CD8^+$ WT1-specific T-lymphocyte responses also associated with those of IFN-γ^+ KLH-specific $CD8^+$ T-lymphocytes. These associations are compatible with the importance of antigen-targeted helper functions for the induction of optimal CTL activity [10] and with the phenomenon of heterologous

Table 1 Clinical responses and overall survival by patient group

	GBM	MBC	MPM	Other*
Clinical response at T1				
CR (%)	0/13 (0%)	0/12 (0%)	0/10 (0%)	0/4 (0%)
PR (%)	1/13 (7.7%)	0/12 (0%)	0/10 (0%)	1/4 (25%)
SD (%)	8/13 (61.5%)	6/12 (50%)	7/10 (70%)	2/4 (25%)
PD (%)	4/13 (30.8%)	6/12 (50%)	3/10 (30%)	1/4 (25%)
ORR	1/13 (7.7%)	0/12 (0%)	0/10 (0%)	1/4 (25%)
DCR	9/13 (69.2%)	6/12 (50%)	7/10 (70%)	3/4 (75%)
Clinical response at T2				
CR (%)	0/13 (0%)	0/12 (0%)	0/10 (0%)	1/4 (25%)
PR (%)	3/13 (23.1%)	0/12 (0%)	0/10 (0%)	1/4 (25%)
SD (%)	3/13 (23.1%)	6/12 (50%)	4/10 (40%)	1/4 (25%)
PD (%)	7/13 (53.8%)	6/12 (50%)	5/10 (50%)	1/4 (25%)
Death (%)	0/13 (0%)	0/12 (0%)	1/10 (10%)	0/4 (0%)
ORR	3/13 (23.1%)	0/12 (0%)	0/10 (0%)	2/4 (50%)
DCR	6/13 (46.2%)	6/12 (50%)	4/10 (40%)	3/4 (75%)
Clinical response at T1 ± T2				
ORR	3/13 (23.1%)	0/12 (0%)	0/10 (0%)	2/4 (50%)
DCR	9/13 (69.2%)	9/12 (75%)	7/10 (70%)	4/4 (100%)
DCR without cancer Tx at T1 ± T2	1/13 (7.7%)	3/12 (25%)	7/10 (70%)	3/4 (75%)
DCR without other Tx at T1 ± T2	1/13 (7.7%)	2/12 (16.7%)	7/10 (70%)	2/4 (50%)
Overall survival[#]				
N patients alive (%)	0/13 (0%)	0/12 (0%)	0/10 (0%)	2/4 (50%)
Median OS from V1 (range), mo	23.5 (5.0–56.4)	26.7 (8.4–58.3)	28.2 (5.6–63.0)	
Median OS from Dx (range), mo	43.7 (13.8–70.4)	41.9 (14.5–117.7)	48.8 (21.8–134.8)	
Frequency of OS > Reference	12/13	7/12	9/10	
$HR^-/HER2^-$ MBC		3/4		
$HR^+/HER2^-$ MBC		2/5		
$HER2^+$ MBC		2/3		

= observed survival calculated from V1 or from diagnosis until death or up to December 31, 2023

Abbreviations: GBM = glioblastoma multiforme. MBC = metastatic breast cancer. MPM = malignant pleural mesothelioma. Other = mixed cohort of other tumor types. T1 = 8 weeks after the start of vaccination. T2 = 6 months after the start of vaccination. CR = complete remission. PR = partial response. SD = stable disease. PD = progressive disease. ORR = overall response rate (CR, PR). DCR = disease control rate (CR, PR, SD). T1 ± T2 = T1 and/or T2. Tx = treatment (cancer Tx = chemotherapy, radiotherapy, and/or tumor surgery; other Tx = chemotherapy, radiotherapy, (tumor) surgery, antihormonal treatment, and/or monoclonal antibodies). N = number of. OS = overall survival. V1 = first *WT1*-mRNA/DC vaccination. mo = months. Dx = diagnosis (for MBC = diagnosis of metastatic disease). OS > Reference = OS higher than expected median OS based on historical controls reported in the literature [3–5].

*SOL02 died prematurely (before *WT1*-mRNA/DC vaccination) and was excluded from the analysis

$CD8^+$ T-lymphocyte helper functionality, which can stimulate tumor-specific CTL responses induced by cancer immunotherapy [11].

In summary, our early-phase clinical study has demonstrated the safety, feasibility, type 1 immunogenicity and clinical activity of adjuvant *WT1*-mRNA/DC vaccination in patients with various solid tumors, and suggests a potential beneficial impact on OS. Antigen-specific type 1 T-lymphocyte response was associated with clinical outcome (disease control and OS). Since this study was performed on a pre-selected group of patients, further clinical studies are warranted to confirm the clinical efficacy of *WT1*-mRNA/DC.

(a)

	WT1										KLH						Antigen-nonspecific					
	CD4+ T-lymphocytes			CD8+ T-lymphocytes					Antibodies		CD4+ T-lymphocytes			CD8+ T-lymphocytes			CD4+ T-lymphocytes			CD8+ T-lymphocytes		
	IFN-γ+	TNF-α+	IL-5+	IFN-γ+	TNF-α+	IL-5+	Tetramer+ total	Tetramer+ ≥2 epit	IgG+ total	IgG+ ≥2 epit	IFN-γ+	TNF-α+	IL-5+	IFN-γ+	TNF-α+	IL-5+	IFN-γ+	TNF-α+	IL-5+	IFN-γ+	TNF-α+	IL-5+
Baseline response	1/39	0/39	0/39	4/39	2/39	3/37	**13/18**	**8/16**	14/37	3/37	0/36	0/36	0/36	6/36	1/36	0/36	1/37	2/37	0/37	13/37	1/37	**27/37**
Post-vaccine response	**23/39**	**22/39**	16/39	**23/39**	15/39	5/39	**12/18**	7/15	9/37	5/37	16/36	**26/36**	6/36	11/36	4/36	5/36	18/37	10/37	8/37	12/37	5/37	7/37
Total # with baseline and/or post-vaccine response	**24/39**	**22/39**	16/39	**25/39**	17/39	8/39	**17/18**	**14/16**	**20/37**	7/37	16/36	**26/36**	6/36	14/36	5/36	5/36	**19/37**	12/37	8/37	**20/37**	6/37	**31/37**

(b)

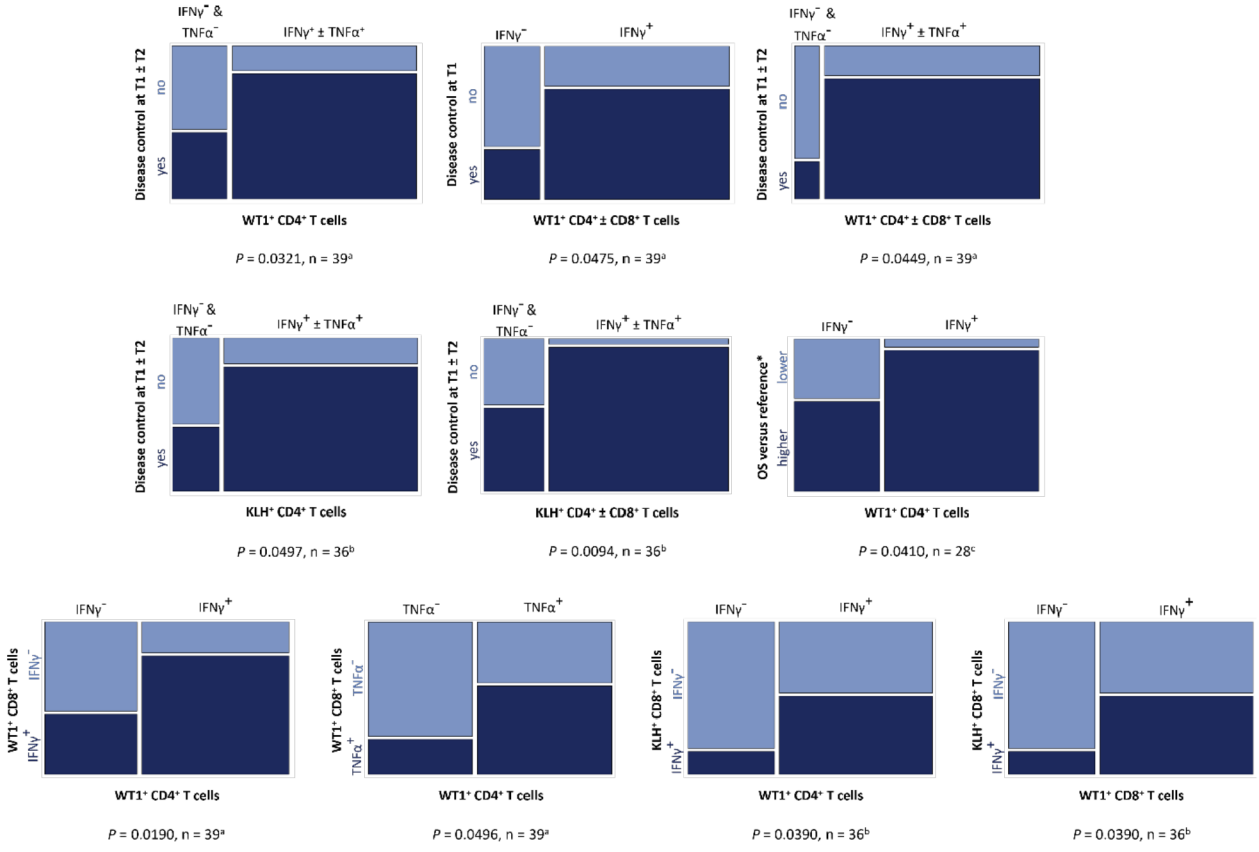

Fig. 1 (See legend on next page.)

(See figure on previous page.)

Fig. 1 Proportions of patients with WT1-specific, KLH-specific, and antigen-nonspecific immune responses (**a**) and statistical associations among immunological and clinical parameters (**b**). (**a**) Responses were determined using intracellular cytokine staining of $CD4^+$ and $CD8^+$ T-lymphocytes, by WT1-specific HLA-A*02:01 tetramer staining of $CD8^+$ T-lymphocytes and by measuring the production of IgG antibodies against WT1. Antigen-nonspecific responses were determined after culture with control medium. Baseline response is defined as values at the PRE time point > 0.1% of $cytokine^+$ $CD4^+$ or $CD8^+$ T-lymphocytes (KLH-responsive or WT1-responsive cases were counted if PRE $cytokine^+$ values were at least 50% higher than PRE antigen-non-specific values); or percentage of WT1 HLA-A*02:01 $tetramer^+$ $CD8^+$ T-lymphocytes > 0.1% at the PRE time point; or values at PRE > 0.15 for WT1 IgG concentrations in the ELISA. Post-vaccine response was defined as increase of at least 50% in response to WT1 (response to non-KLH-exposed *WT1*-mRNA/DCs and/or to the WT1 peptide pool) or to KLH or to control medium at the POST and/or FIN time points compared with the PRE time point (as defined in Additional File 1: Methods); or increase of at least 50% in the percentage of WT1 HLA-A*02:01 $tetramer^+$ $CD8^+$ T-lymphocytes at the POST and/or FIN time points compared with the PRE time point (as defined in Additional File 2: Figure S2); or increase in WT1 IgG concentrations from below (in PRE) to above (in POST and/or FIN) the cutoff absorbance value of 0.15 in the ELISA or increase in WT1 IgG concentrations of at least 50% at the POST and/or FIN time points (as defined in Additional File 1: Methods) from a PRE value of > 0.15 in the ELISA. Numbers in bold indicate where ≥ 50% of patients examined showed a response. (**b**) Statistical analysis of the data summarized in Table 1 and Fig. 1a was performed to assess associations between clinical response and immune response parameters or between immune response parameters. Each mosaic plot represents a statistically significant 2 × 2 contingency analysis (Additional File 1: Methods) between the parameters indicated. *P* values are indicated under the mosaic plot

[a] = 13 patients with glioblastoma multiforme (GBM), 12 patients with metastatic breast cancer (MBC), 10 patients with malignant pleural mesothelioma (MPM), and 4 patients with other tumors

[b] = 12 patients with GBM, 11 patients with MBC, 9 patients with MPM, and 4 patients with other tumors

[c] = 13 patients with GBM, 5 patients with $HR^+/HER2^-$ MBC, and 10 patients with MPM

* GBM OS from diagnosis > 16.0 months vs. ≤16.0 months & $HR^+/HER2^-$ MBC OS from diagnosis of metastatic disease > 42.1 months vs. ≤42.1 months & MPM OS from diagnosis > 23.4 months vs. ≤23.4 months

Abbreviations: WT1 = W1-reactive. KLH = KLH-reactive. $CD4^+$ = reactivity in $CD4^+$ T-lymphocytes. $CD8^+$ = reactivity in $CD8^+$ T-lymphocytes. IFN-γ^+ = interferon-γ production. TNF-α^+ = tumor necrosis factor-α production. IL-5^+ = interleukin-5 production. ≥2 epit = number of cases positive for 2 or more WT1 epitopes. # = number of patients. ± = and/or. + = reactivity. − = no reactivity. n = number of patients analyzed. OS = overall survival

Abbreviations

CR	Complete remission
CTL	Cytotoxic T-lymphocyte
DC	Dendritic cell
DCR	Disease control rate
GBM	Glioblastoma multiforme
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
IFN	Interferon
IL	Interleukin
KLH	Keyhole limpet hemocyanin
MBC	Metastatic breast cancer
Mo	Months
MPM	Malignant pleural mesothelioma
mRNA	Messenger RNA
ORR	Overall response rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PR	Partial response
SD	Stable disease
TNF	Tumor necrosis factor
WT1	Wilms' tumor protein
WT1-mRNA/DC	Autologous DC loaded by mRNA electroporation with the Wilms' tumor protein WT1

Supplementary Information

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Additional File 1. Methods

Additional File 2. Supplementary tables & figures

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Author contributions

ZNB was the promotor and PG, MTH, ALVdV, VFVT, and MP were the copromotors of the project. ZNB, GN, PVD, VFVT, MP, SAnguille, and ELJMS supervised and supported the clinical study. ZNB, PG, MTH, YW, JVdBrande, PS, SAltintas, PAvD, IV, ALVdV, MP, and SAnguille recruited and/or treated the patients. MMC supervised the leukapheresis procedures. GN, BS, KC, and ML organized the production and quality control of the DCs. HDR, NC, and BS carried out the immunological analyses of patient samples. SL-L and DAP provided critical reagents (WT1-specific peptide-HLA-A*02:01 tetramers). YOka, YOji, and HS conceptually inspired this study and performed the WT1 IgG assays. ZNB, MDL, EL, JVdBossche, DAP, YOka, YOji, HS, and SAnguille analyzed the immune response data. AS and BOdB analyzed the radiological response. ZNB, MDL, YW, KS, LR, and SAnguille collected the clinical data. GO performed a critical literature search. ZNB, MDL, EL, HDR, JVdBossche, and SAnguille performed the statistical analyses. ZNB, MDL, YW, and SAnguille wrote the manuscript with input from DAP. MDL and SAnguille designed the figures.

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Data availability

All data generated and/or analyzed during the course of this study are included in the main article and supplementary information.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Antwerp University Hospital/University of Antwerp (EC 10/40/266) and the Belgian Federal Agency for Medicines and Health Products (FAGG 08 − 0005) and registered at ClinicalTrials.gov (NCT01291420) and EudraCT (2011-000547-24). The sponsor's protocol code was CCRG 11 − 001. All participants provided informed written consent in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests
VFVT and ZNB are coinventors of a now-elapsed patent covering the messenger RNA electroporation technique (Improved Transfection of Eukaryotic Cells with Linear Polynucleotides by Electroporation, WO/2003/000907).

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