

Treatment of Metastatic Renal Cell Carcinoma With Autologous T-Lymphocytes Genetically Retargeted Against Carbonic Anhydrase IX: First Clinical Experience

TO THE EDITOR: Adoptive transfer of autologous T-lymphocytes that are gene transduced to express antigen-specific receptors represents an experimental therapy to provide tumor-specific immunity to cancer patients. We studied safety and the proof of this concept in patients with metastatic renal cell carcinoma (RCC), and have encountered toxicity that is likely to be antigen specific.

We have constructed a single-chain antibody-type (scFv) –receptor based on murine monoclonal antibody (mAb) G250.¹ This mAb recognizes an epitope on carboxy-anhydrase-IX (CAIX), which is frequently overexpressed on clear cell RCC. Following retroviral introduction of the *scFv(G250)* transgene into primary human T-cells, the scFv(G250) receptor is expressed on the surface of these cells, which enables them to recognize CAIX and to exert antigen-specific effector functions, such as cytokine production after exposure to CAIX and the killing of CAIX⁺ RCC cell lines.^{2,3}

We treated patients with scFv(G250)-transduced T-cells in an inpatient dose-escalation scheme of intravenous (IV) doses of 2×10^7 cells at day 1; 2×10^8 cells at day 2; 2×10^9 cells at days 3 through 5 (treatment cycle 1); and 2×10^9 cells at days 17 to 19 (treatment cycle 2), in combination with human recombinant interleukin-2 (IL-2; Chiron Corporation, Amsterdam, the Netherlands), subcutaneously, 5×10^5 U/m² twice daily administered at days 1 to 10 and days 17 to 26. This protocol was approved by the governmental regulatory authorities and the institutional medical ethical review board. Adaptations to this protocol were implemented only after approval by these boards. Written informed consent was obtained from all patients.

In this letter, we report on the clinical experiences of the first three patients. The patients had CAIX⁺ metastatic clear cell RCC, had undergone tumor nephrectomy, and had progressive disease after 6 to 17 months of interferon alfa (IFN- α) treatment. From all, we successfully generated functional scFv(G250)⁺ T-cells *ex vivo* (Table 1). Infusions of these gene-modified T-cells were initially well-tolerated. However, after four to five infusions, liver enzyme disturbances reaching National Cancer Institute Common Toxicity Criteria grades 2 to 4 developed. These toxicities necessitated the cessation of treatment in patient 1 and patient 3, corticosteroid treatment in patient 1, and reduction of the maximal T-cell dose to 2×10^8 T-cells in patient 2 and patient 3. After treatment, patients showed progressive disease between 36 and 106 days. In order to elucidate the underlying mechanisms accounting for the liver toxicity, a liver biopsy was performed on patient 1, showing a discrete cholangitis with T-cell infiltration around the bile ducts, and CAIX expression on the bile duct epithelial cells. Although technical limitations prohibited direct identification of

scFv(G250)⁺ T-cells in these sections, these findings strongly suggest that the liver toxicity is caused by a specific attack of the scFv(G250)⁺ T-cells against the CAIX⁺ bile duct epithelial cells.

We transiently detected both scFv(G250)⁺ T-cells and scFv(G250) DNA copies in the circulation of all three patients from day 3 of treatment onward, using flow cytometry and quantitative real-time polymerase chain reaction (PCR). The time period during which the transduced cells were detected in the circulation depended on the method used, that is, up to 32 days by flow cytometry and up to 53 days by PCR⁴ (Table 1).

Before treatment, peripheral blood mononuclear cells did not show scFv(G250)-mediated functions, that is, specific cytolysis of CAIX⁺ target cells and production of IFN- γ on stimulation with such cells. After infusions of scFv(G250)-transduced T cells, these activities became detectable in all three patients (Table 1).

All three patients developed low levels of anti-scFv(G250) antibodies between 37 and 100 days after the start of T-cell therapy, which were directed against the G250 idiotype (id). Remarkably, these responses were less frequent in RCC patients treated with weekly IV infusions of 50 mg chimeric G250 mAb (ie, in 6% to 30% of patients),^{5,6} indicating that the expression of scFv(G250) on the cell membrane of T-cells elicits a relatively efficient immune response against the murine G250-id. Such response may hamper the effective clinical use of murine-human chimeric receptors, and may require construction of receptors from completely human mAbs.

In summary, our data show clear *in vivo* reactivity of autologous T-cells that have been genetically retargeted using a single-chain antibody-type receptor. The observed liver toxicity is most likely due to the reactivity of transduced T-cells against the target antigen expressed on normal tissue, that is, the epithelial cells lining the bile ducts, and thereby hinders administration of T-cells in numbers that can be expected to yield antitumor activity. We consider our observations, together with those from T-cell therapies directed against self-antigens,^{7,8} relevant for other studies involving T-cell retargeting for therapeutic purposes. Ideally, the target antigens for such studies should be carefully chosen, so as to be expressed only by malignant cells and not by normal cells.

Alternatively, strategies need to be developed to attenuate activity of retargeted T-cells against normal tissues expressing target antigen to circumvent the observed adverse events.

In order to prevent liver toxicity in future patients, we have modified our clinical protocol into a conventional phase I study, and have included an infusion of 5 mg cG250 antibody 3 days before the first infusion of gene-modified T-cells. The rationale of this amended protocol is that repeated administration of cG250 has not only been shown to be clinically safe and well-tolerated by more than 200 patients,⁹ but more importantly, cG250 localizes to RCC metastasis but not to the liver, after having saturated uptake by liver tissue (but not RCC metastasis) by a single low dose of cG250.^{6,10,11} By pretreating patients with a single, low dose of cG250, we aim to protect the bile duct epithelium from the damaging effects exerted by scFv(G250)⁺

Table 1. Characteristics of Preinfusion scFv(G250)-Transduced T-Cells and of Peripheral Blood Following Immunogene Therapy

Parameter	Patient 1	Patient 2*	Patient 3*
Preinfusion characteristics of scFv(G250)-transduced T-cells			
Cell and DNA copy counts			
No. of infusions	4†	5/3‡	4†
Total No. of T-cells ($\times 10^9$)	3.99	0.8/0.59	0.60
Mean % scFv(G250) ⁺ T-cells	53	52/76	63
Total No. of scFv(G250) ⁺ T-cells ($\times 10^9$)	2.13	0.43/0.42	0.38
Mean No. of scFv(G250) DNA copies per scFv(G250) ⁺ T-cell	2.3	4.5/6.8	2.8
scFv(G250)-mediated functions			
CAIX-specific cytotoxicity (LU ₂₀)§			
LU ₂₀ /10 ⁶ scFv(G250) ⁺ T-cells	372	104/82	88
Total LU ₂₀	792, 204	78, 774	33, 274
CAIX-specific IFN- γ production, ng per 10 ⁶ scFv(G250) ⁺ T-cells per 24h	33	33/24	28
Characteristics of peripheral blood samples during immunogene therapy			
Circulating scFv(G250) ⁺ T-lymphocytes			
Peak, day	7	10/21	6
Peak level, cells/ μ l	5.3	2.7/1.6	0.8
Period during which cells detectable	3-23	3-32	3-7
Circulating scFv(G250) DNA copies			
Peak, day	tfd	17/19	8
Peak level, cells/ μ l	tfd	7.1/5.2	5.3
Period during which DNA detectable	tfd	tfd-53	3-32
Human anti-scFv(G250) antibodies			
Day of first appearance	37	100	79
Peak, day	57¶	100¶	79
Peak level, ng/ml	706	190	292
ScFv(G250)-mediated functions in vitro			
CAIX-specific cytotoxicity			
Peak, day	8	8/22	5
Peak level, LU ₂₀ /10 ⁶ PBMC	16	29/44	26
CAIX-specific IFN- γ production			
Peak, day	8	8/22	5
Peak level, ng/ml per 10 ⁶ PBMC per 24h	9	25/32	37

Abbreviations: scFv, single-chain antibody type; LU, lytic unit; CAIX, carboxy-anhydrase IX; IFN, interferon; h, hour; PBMC, peripheral blood mononuclear cells; tfd, too few data points to allow data assessment.

*T-cell dose reduced to a maximum of 2×10^8 T-cells.

†Treatment cycle 1 only.

‡Treatment cycle 1/treatment cycle 2.

§One LU₂₀ is defined as the number of effector T-cells required to lyse 20% of 2,500 CAIX target cells in a 4 h ⁵¹Cr release assay.

||Day(s) after start of treatment (day 1 = day of first infusion).

¶Last day of observation.

T-cells. The Dutch regulatory authorities have approved this amended protocol and accrual of patients is currently ongoing.

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