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Phase I Dose Escalation Study of Sodium Stibogluconate (SSG), a Protein Tyrosine Phosphatase Inhibitor, Combined with Interferon Alpha for Patients with Solid Tumors

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Abstract

Purpose: Sodium stibogluconate (SSG), a small molecule inhibitor of protein tyrosine phosphatases, combined with IFN-alpha-2b (IFN-α) inhibited solid tumor cell line growth *in vitro*. We conducted a phase I clinical trial with SSG plus IFN-α in advanced cancer patients to assess tolerance, maximum tolerated dose (MTD) and immune system effects.

Experimental Design: SSG was administered intravenously alone for five days of week 1, cycle 1 (21 days per cycle) and together with IFN-α 2b s (3 million units sc TIW) in week 2, and after a rest during week 3, on a 2-week on/1-week off cycle. SSG dose levels were 400, 600, 900, 1125, and 1350 mg/m^2.

Results: Twenty-four patients were studied. Common toxicities included asymptomatic elevated serum lipase, thrombocytopenia, fatigue, fever, chills and anemia. The dose-limiting toxicities (DLT) were hypokalemia, thrombocytopenia, fatigue, pancreatitis and skin rash. The MTD was 900 mg/m^2 SSG and IFN-α, 3 million units TIW. At this dose, patients had a significantly lower number of regulatory T cells (T$_R$ Cells) (p = 0.012), myeloid dendritic cells (mDC) (p = 0.028); higher percentage of natural killer (NK) cells that synthesized perforin (p = 0.046) and of plasmacytoid dendritic cells (pDC) that secreted IFN-α (p = 0.018) in response to activation through toll-like receptor (TLR) 7 and TLR 8 by CL097, the highly water-soluble derivative of the imidazoquinoline compound R848.

Conclusions: SSG in combination with IFN-α 2b was well tolerated and augmented cellular immune parameters.

Key words: sodium stibogluconate, phase 1, interferon alpha, immunity, cancer

INTRODUCTION

Sodium stibogluconate (SSG), a small molecule inhibitor of protein tyrosine phosphatases (PTPases) [1], has been used extensively for the treatment of human leishmaniasis [2,3] and preclinically with demonstrable activity against a murine melanoma cell line [3]. SSG putatively interferes with SHP-1, so that

IFN-alpha (IFN-α) remains in the "on" state and inhibits tumorigenesis [4]. IFN-α 2b is FDA-approved for treating solid tumors such as malignant melanoma [5] and AIDS-related Kaposi's sarcoma [6], and hematologic malignancies such as aggressive follicular non-Hodgkin's lymphoma and chronic myelogenous leukemia [7]. However, tumor cell resistance and side effects often limit its clinical efficacy, which is expected to improve at a lower dose and when combined with other therapeutic agents [8,9].

The combination of SSG and IFN α-2b was shown to be effective against larger WM9 tumors in mice and was well tolerated in a long-term treatment course [1]. These preclinical observations suggested an important potential for PTPase inhibitors to improve the efficacy of IFN α-2b. Sodium stibogluconate is an ideal drug to evaluate as an antineoplastic agent in combination with IFN α-2b. We hypothesized that combining SSG and IFN-α 2b would modulate host-immune defense mechanisms and enhance antitumor activity in cancer patients with tumors known to be responsive to IFN-α therapy. Our goals in this phase I, dose-finding study were to investigate the synergistic antitumor activity of the combination of SSG and IFN-α 2b, delineate the toxicity profile, establish the maximum tolerated dose (MTD), and immune effects in cancer patients.

PATIENTS AND METHODS

### Patient eligibility and selection

Inclusion criteria included metastatic or locally advanced solid cancers not responsive to conventional therapy with no established life-prolonging therapy available; age ≥18 years; Eastern Cooperative Oncology Group (ECOG) (performance status 0–2; adequate bone marrow; adequate hepatic status, renal function (creatinine ≤1.5 mg/dL) and cardiac function (ejection fraction >50%); no chemotherapy or radiotherapy 3 weeks before study entry. Exclusion criteria included concurrent immunotherapy, no recovery from acute toxicity of previous therapy, medically uncontrolled cardiovascular illness, electrocardiogram anomalies suggestive of cardiac conduction delay (QTc > 0.47 seconds), past clinically significant cardiac arrhythmias, symptomatic or untreated central nervous system metastases and history of hypersensitivity to IFN-α 2b or SSG or their components.

Treatment/study plan

Sodium stibogluconate (Lenocta™) was supplied by VioQuest Pharmaceuticals, Inc. (Basking Ridge, NJ). Prior to enrollment, patients signed a written, informed consent in accordance with NCI require-

ments, the MD Anderson Cancer Center Institutional Review Board and the University of New Mexico (UNM) School of Medicine Human Research Review Committee policies.

Cohorts of 3 patients each were enrolled using a standard phase I, 3+3 study design. Each cycle consisted of 21 days. During the first week of cycle 1, patients received SSG alone intravenously (IV) over 15 minutes for 5 days (Monday through Friday) (Figure 1). In week 2, cycle 1, patients received SSG IV for 5 days (Monday through Friday), along with 3×10^6 units of IFN-α 2b subcutaneously (SQ) three times a week (Monday, Wednesday, Friday). Week 3, cycle 1, was a rest period. During cycle 2 and subsequent cycles, patients received SSG IV for 5 days and IFN-α 2b SQ thrice weekly for the first and second weeks of each cycle. The SSG dose was escalated in successive cohorts, with no escalation within cohorts. Cycles continued until disease progression or dose-limiting toxicities(s) (DLT).
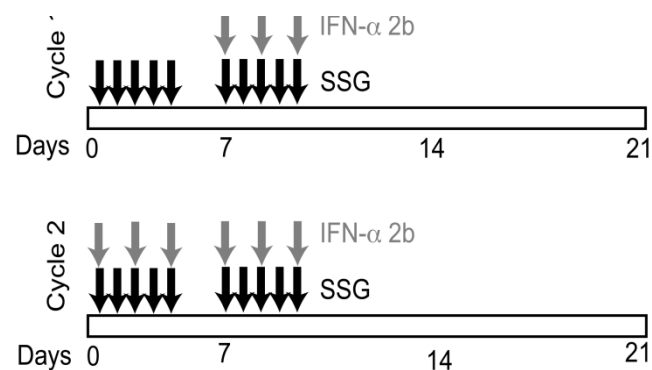
Figure 1. Study design and treatment regimen. SSG was administered daily as a monotherapy during the first week of cycle 1. Peripheral blood samples were collected prior to therapy on the second week of cycle 1 (C1D8) to evaluate the effect of SSG. IFN-α 2b was administered 3 times per week beginning the second week of cycle 1. Peripheral blood samples were collected at the end of 2 cycles (C2D12) to evaluate the effect of SSG + IFN-α 2b combination therapy.

Toxicity in each group of 3 patients treated with different dosage levels was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, at the end of each cycle. Even though the traditional definition of DLTs within the first cycle was initially used, we later extended our DLT window to cycle 2 as the cycles were relatively short and only SSG was given during the first week of the first cycle. DLT was defined as any one or more of

the following events considered related to treatment with study drug that were grade >3: non-hematologic toxicity, grade 4 hematologic toxicity (neutropenia, anemia or thrombocytopenia), prolongation of QTc to >0.47 seconds, grade 2 or greater cardiovascular arrhythmia, and/or ECG changes associated with T wave inversion with ST segment depression, any grade 4 pancreatic enzyme elevation that lasted longer than 8 days or that was accompanied by clinical symptoms of pancreatitis.

A grade 3 non-hematologic toxicity or grade 4 hematologic toxicity was considered a DLT only after delivery of maximum supportive care. Important medical events other than those listed above were considered a DLT based upon appropriate medical judgment and following discussion among the investigators and the VioQuest medical monitor.

Dose escalation

The starting dose of SSG was 400 mg/m²/day administered daily IV over 15 minutes. With no significant toxicity, the dose for subsequent cohorts was increased by 50% of the preceding dose. If DLTs occurred, the dose in subsequent cohorts was increased by only 25% of the preceding dose. Cohorts of at least 3 patients were treated at each dose level until the MTD was defined. If 1 of 3 patients had a DLT, the cohort was expanded to a maximum of 6 patients. If only 1 of those 6 patients experienced a DLT, the dose for subsequent cohorts was escalated by 25%. If at least 2 patients in a cohort had DLTs, no dose escalation was permitted. The dose level at which 2 of 6 patients experienced a DLT was considered one dose level above the MTD. Table 1 shows the dose escalation scheme for this study.

Table 1: Dose Escalation Schedule for SSG and Fixed Dose of IFN-α 2b (3 x 10^6 units) (N = 24 patients)

Dose of SSG (mg/m²)	N =	DLTs
400	3	0
600	5	0
900 (expansion cohort)	8	0
1125	4	3 (symptomatic pancreatitis and thrombocytopenia)
1350	4	2 (hypokalemia, thrombocytopenia, fatigue and skin rash)

Duration of therapy

Patients remained on protocol until disease progression, unacceptable adverse events, concurrent illness preventing further administration of drug, or if they had stable disease (SD), a partial response (PR), or a complete response (CR) to treatment, and if there

was an acceptable toxicity profile. Patients were taken off study for therapy-related intolerable toxicity, progressive disease, or self-election to withdraw from study.

Clinical response

All patients underwent imaging with computed tomography (CT) scans and/or positron emission tomography (PET), and disease-specific tumor markers whenever applicable. Evaluation for treatment response was done every six weeks using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [10].

Immune monitoring of patients

Patients were assessed prior to initiation of SSG therapy, cycle 1, day 1 (C1D1), at the end of SSG monotherapy (C1D5) and prior to addition of IFN-α on C1D8, at the end of the combination therapy (C1D12), and on C2D12. On days of assessment, patients provided 27 mL of peripheral blood for immune evaluation that included leukocyte immunophenotyping, cytokine syntheses by individual T cells activated through the T-cell receptor (TCR) using anti-CD3 antibodies and by toll-like receptor (TLR)-activated dendritic cells (DC); expression of granzyme B and perforin A by natural killer (NK), natural killer T (NKT) cells, and CD8$^+$ T cells.

Enumeration of leukocyte subsets by flow cytometry

Subsets of T cells (CD4, CD8, and T-regulatory (T_R)), B-cells (CD19), and NK cells (CD56/16) cells were determined as previously described [11].

Perforin A and Granzyme A expression by NK and NKT cells

Briefly, peripheral blood lymphocytes were stained for cell surface markers CD3, CD16$^+$56, and CD8 as previously described [11], then permeabilized with BD CytoFix/CytoPerm according to the manufacturer's recommended procedures and stained with FITC conjugated antibodies against granzyme A, perforin or the appropriate isotype-matched control immunoglobin, and analyzed using 6-parameter flow cytometry. Perforin and granzyme expression was recorded as percentage of CD16/56$^+$ (NK) or CD3$^+$16/56$^+$ (NKT) lymphocytes with fluorescent intensity of the perforin or granzyme antibodies greater than isotype-matched control antibodies.

Cytokine synthesis by anti-CD3 activated T cells

Intracellular cytoplasmic interleukin (IL)-2, IL-10, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) by TCR-activated T cells were

measured by a flow cytometric assay as previously described [12].

Quantification of circulating DCs

Subsets of myeloid DCs (mDC/DC1) and plasmacytoid DCs (pDC/DC2) were enumerated as previously reported [13].

Cytokine synthesis by mDC and pDC activated through TLR

Cytokine synthesis by DCs stimulated with 10 µM of CL097, a highly water-soluble derivative of the imidazoquinoline compound R848 (Invivogen, San Diego, CA), was performed as previously described [14]. Similar to R848, CL097 is a TLR7 and TLR8 ligand that induces cytokine syntheses in DCs through the activation of the NF-κB [15,16].

Statistical analysis

Descriptive statistics were used for the patient treatment description. Due to small sample size and non-normal distribution of cytokine production, nonparametric tests compared median values for immunologic analysis. The Friedman test assessed significant rank differences in phenotype and cytokine measures over the study period followed by the Wilcoxon signed-rank test of paired samples to determine differences between specific time points in therapy. The Mann-Whitney U test analyzed differences among different treatment arms, i.e., low-dose SSG (<900 mg/m^2) and high-dose (≥900 mg/m^2). Graphs were plotted as mean plus or minus standard error to show central tendency and variance.

RESULTS

Patient characteristics

Twenty-four patients (13 men and 11 women) participated in this phase I study (median age of 59.5 years; range, 37-82). Nine patients had an ECOG performance status of 0, and 15 patients had an ECOG of 1. Prior therapies varied from 1 to 10 regimens (median, 4). Various solid tumors were included; most commonly melanoma, pancreatic and colorectal (Table 2).

Dose escalation and MTD

Within the SSG 900 mg/m^2 cohort, one patient progressed during cycle 1 and was replaced. Because three evaluable patients tolerated the 900 mg/m^2 SSG dose, it was increased to 1350 mg/m^2, and two patients experienced DLTs. The first patient with DLT had a grade 4 hypokalemia and a grade 4 thrombocytopenia (which did not return to baseline after platelet transfusion). The second patient with DLT

had grade 3 fatigue and grade 3 skin rash. Subsequently, an intermediate dose of SSG of 1125 mg/m^2 was tested. One patient in this cohort had a grade 2 DLT of clinically symptomatic pancreatitis and the cohort was expanded. Two additional patients had grade 2 pancreatitis and grade 4 thrombocytopenia. Thus, the MTD was set at 900 mg/m^2. The cohort was expanded to total of 8 patients. No DLTs were observed.

Table 2: Patient Characteristics (N = 24)

Total Pts	24			
Median Age	59.5			
Range	37-82			
Male	13			
Female	11			
Race				
White	22			
Asian	1			
Hispanic	1			
ECOG				
PS= 0	9			
PS=1	15			
Media Prior Regimens	4			
Max	10			
Min	1			
Diagnosis	Number	%	Dosage	Patients
Melanoma	7	29	400	3
Pancreatic	4	17	600	5
Colorectal	3	13	900	8
Adenocystic H&N	2	8	1125	4
Mesothelioma	1	4	1350	4
Prostate	1	4		
Neuroendrocrine	1	4	Total	24
Ovarian	1	4		
Squamous Cell H&N	1	4		
Granulosa Cell	1	4		
Merkel Cell	1	4		
Angiosarcoma	1	4		
Total	24	99		

PS , performance status; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck

Safety/Toxicity

Adverse events are shown in Table 3. Despite elevated serum amylase (n=7) and/or lipase (n=16) levels occurring frequently, most patients were asymptomatic; two had clinically significant grade 2 pancreatitis. Fourteen patients completed two cycles and were restaged. One patient with advanced refractory colorectal cancer in the 600 mg/m^2 SSG cohort received cycle 3, but withdrew from the study.

The second patient with adenocystic carcinoma in the 1350 mg /m² SSG cohort, also with SD, withdrew from the study due to non-DLT side effects and treatment schedule. A third patient with ocular melanoma in the 400 mg /m² SSG cohort had SD after two cycles, but withdrew from treatment. The other 11 patients had progressive disease at restaging at the end of cycle 2. Although there was no clinically observable anticancer activity in this study, SSG had significant effects on host-immune responses.

Table 3: Drug Related Common Side Effects

| | Side Effects at Different Dose Levels | | | | | | | | | | | | | | | | | |
| | TOTAL DLTS | | | 400 mg/m² | | | 600 mg/m² | | | 900 mg/m² | | | 1125 mg/m² | | | 1350 mg/m² | | |
Grade	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4
Nausea	6	0	0	1			1			2			1			1		
Vomiting	4	0	0	1						1			1			1		
Chills	9	1	0	2			4			1			1			1	1	
Fatigue	7	4	0	2	1		3			1	1			1		1	1	
Fever	10	1	0	1			5			2			1			1	1	
Myalgia	3	0	0				2									1		
Rash	1	1	0										1				1	
Anorexia	5	1	0				1			2	1		1			1		
Lymphopenia	4	0	0				4											
Leukocytes	4	1	0				1			1	1					2		
Neutrophils	5	0	0				1			2						2		
Platelets	3	5	3					1		3	1			2		3	3	1
Hemoglobin	3	7	0		1					1	5					2	1	
Amylase	3	4	0	1			1	1		1	1		1			1		
Lipase	4	7	5			1	1	2	1	2	3	1		1		1	2	1
Potassium, Serum Low	2	4	2							1	2	1		2		1		1
Pancreatitis	2	0	0										2					

### Enumeration of leukocyte subsets by flow cytometry

Seventeen patients were evaluated for immune studies. For the immunology data analysis, patients who received SSG <900 mg/m² (n=8) were defined as the low-dose SSG cohort, and patients who received a dose of SSG ≥900 mg/m² were defined the high-dose SSG cohort (n=9).

Initially, the effect of SSG monotherapy, C1D1 vs. C1D8, and the effect of SSG in combination with IFN-α (C1D8 vs. C2D12) were assessed in all patients. After SSG monotherapy, median %T_R cells (p = 0.022) (Figure 2), median %mDC (p = 0.003) (Figure 3A) and median %pDC (p = 0.022) (Figure 3B) significantly decreased, but following combination therapy median %mDC (p = 0.041) significantly increased (Figure 3A). In patients receiving low-dose SSG monotherapy, there were statistically significant reductions in the median %CD4+ T cells (43.7% vs. 41.1%, p = 0.036) and median %T_R cells (2.5% vs. 2.0%, p = 0.017), but statistically significant increases in median %NK cells (17.6% vs. 22.3%, p =0.05). Following combination therapy the median %mDC increased (47.8% vs. 58.3%, p = 0.028). However, in patients receiving high-dose SSG there were no statistically significant changes in median %CD4+ T (49.0% vs. 49.9%, p = 0.575), median %T_R cells (3.4% vs. 3.0%, p = 0.444), and median %NK cells (16.6% vs. 14.4%, p = 0.721).

Following combination therapy the median %mDC increased in patients receiving low-dose SSG (47.8% vs. 58.3%, p = 0.028), and although there was a similar trend in patients receiving high-dose SSG, it was not statistically significant (45.0% vs. 55.0%, p = 0.893).
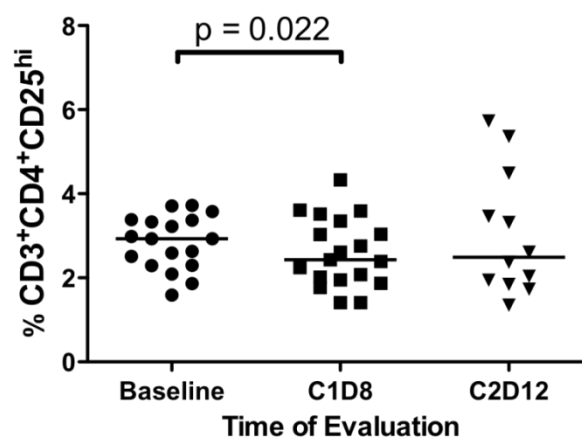
Figure 2 Differences in the percentage of CD4+CD25^{hi} T$_R$ cells. Fresh peripheral blood samples were evaluated by flow cytometry for the presence of CD3+CD4+CD25^{hi} T$_R$ cells at baseline, following SSG monotherapy (C1D8), and following SSG + IFN-α 2b combination therapy (C2D12). There was a significant decrease in the percentage of CD3+CD4+CD25^{hi} T$_R$ cells following SSG monotherapy.
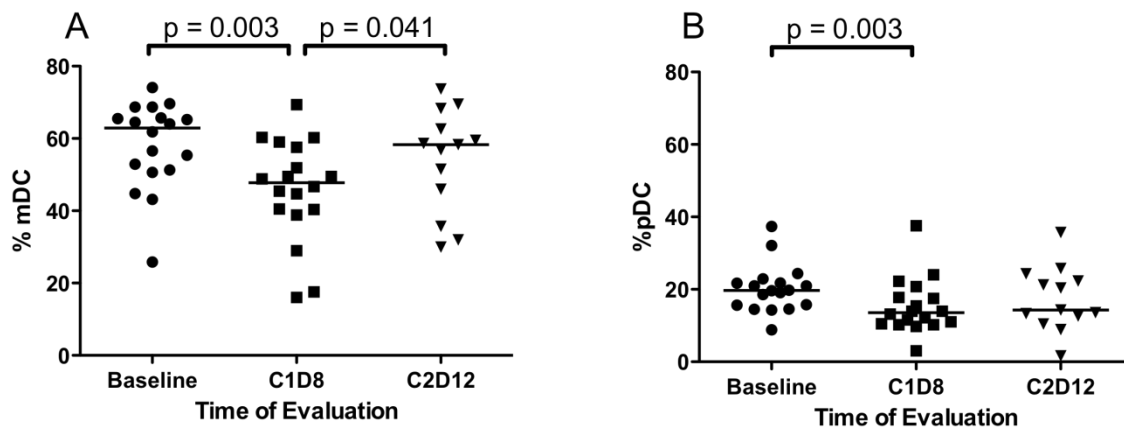
Figure 3 Differences in the percentage of dendritic cells. Fresh peripheral blood samples were evaluated by flow cytometry for the presence of Lin⁻HLA-DR⁺ dendritic cells at baseline, following SSG monotherapy (C1D8) and following SSG + IFN-α combination therapy (C2D12). (A) Following SSG monotherapy, there was a transient decrease in the percentage of CD11c⁺CD123⁻ mDC within the Lin⁻HLA-DR⁺ population followed by a significant increase with the addition of IFN-α 2b. (B) The percentage of CD11c⁻CD123⁺ pDC decrease within the Lin⁻HLA-DR⁺ DC population following SSG monotherapy.
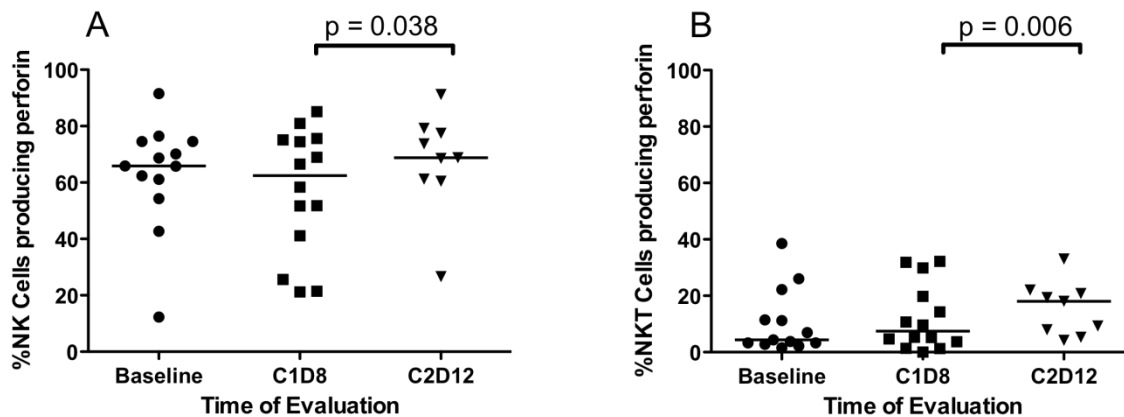
Figure 4 Differences in the percentage of NK and NKT cells that produced perforin A. Fresh peripheral blood samples were evaluated by flow cytometry for the presence of NK and NKT cells with constitutive perforin A. (A) Perforin expression by NK cells is unaffected by SSG monotherapy (C1D8). Following treatment with both SSG and IFN- α 2b (C2D12), there is a significant increase in the percentage of NK cells expressing perforin A. (B) Similarly in CD3+16/56+ NKT cells, perforin A expression was unaffected by SSG monotherapy but was significantly increased by treatment with both SSG and IFN-α 2b (C2D12).

Cytokine production by TLR-activated mDC and pDC

In all patients at the end of SSG monotherapy (C1D8) as well at the end of combination therapy (C2D12), there were no significant changes in %mDC and %pDC that synthesized cytokines following activation with the TLR agonist CL097 (data not shown).

However, patients who received high-dose SSG had statistically significant increased median %pDC that synthesized IFN-α following activation through TLR7 and TLR8 by CL097 (3.15% vs. 9.09%, p = 0.012). When IFN-α 2b was added to this regimen, the percent of pDC that produced IFN-α increased further but not to statistical significance (9.09% vs. 12.98%, p =

0.0465). The syntheses of IL-10, IL-12, and TNF-α by TLR-activated mDC remained unchanged with high-dose SSG monotherapy or following combination therapy of high-dose SSG and IFN-α 2b in both dose groups. Similarly, SSG alone or in combination with IFN-α 2b did not affect the ability of TCR-activated CD4+ T and CD8+ T cells to synthesize cytokines.

Expression of granzyme B and perforin A by NK, NKT, and CD8+ T cells

NK, NKT and CD8+ T cells mediate tumor cell cytotoxicity through expression of granzyme B and perforin A. Data on all patients show that SSG alone did not affect the expression of perforin A and granzyme B in NK, NKT, and CD8+ T cells. Following the addition of IFN-α 2b, there was a statistically significant increase in median %NK cells (62.4% vs. 68.8%, p = 0.038) (Figure 4A) and median %NKT cells (7.4% vs. 18.0%, p = 0.006) (Figure 4B), but not in median CD8+ T cells expressing perforin A. Patients receiving high-dose SSG and IFN-α 2b had a higher %NK cells expressing perforin A (66.5% vs. 75.6%, p = 0.028). No differences were observed in expression of granzyme B by NK, NKT, and CD8+ T cells of patients at either dose of SSG.

DISCUSSION

This phase I study investigated the biological activity of SSG in combination with IFN-α 2b to determine toxicity profile, MTD, and immune system effects. All patients had multiple prior treatments. No clinical responses were observed, despite the known biological activity of SSG in a number of animal experimental systems [17] where SSG alone or in combination with IFN-α 2b, demonstrated antitumor activity against prostate cancer xenografts [18]. In another experiment of SSG plus IL-2, antitumor activity against renal cell carcinoma in mice was enhanced and mediated through an immune mechanism involving IFN-γ [19].

Common toxicities included asymptomatic elevated serum lipase, thrombocytopenia, fatigue, fever, chills and anemia. The DLT were hypokalemia, thrombocytopenia, fatigue, pancreatitis and skin rash.

Patients who received high-dose SSG had a statistically significant decrease in the median percentage of pDC at the end of SSG monotherapy with a concomitant statistically significant increase in the median percentage of pDC that produced IFN-α. At the end of cycle 2, day 12, the median percentages of pDC and pDC producing IFN-α were increased. Plasmacytoid dendritic cells are the most potent producers of IFN-α [20-22]. They greatly influence the differentiation of CD4+ T cells towards TH2 responses by producing IL-10 and inhibiting the production of IL-12 by mDC [23], or enhancing the development of T_R cells, which, in turn, suppresses antigen-specific immune responses [24]. Conversely, IL-12 production by mDC enhances IFN-γ produced by T cells and NK cells and favors a TH1 immune response [25]. Here, low-dose SSG increased pDC activity as measured by the increased median percentage of TLR-activated pDC that produced IFN-α.

IFN-α also stimulates mDC to stimulate IL-12, which in turn stimulates T-cells to secrete IFN-γ, and arms NK cells and CD8+ cytotoxic T lymphocytes (CTL) with perforin A and granzyme B for killing tumor targets. However, increased production of IFN-α by pDC after SSG monotherapy were insufficient to induce expression of perforin A by NK or NKT cells. Only after IFN-α 2b administration did the median percentages of NK cells and NKT cells that expressed perforin A increase. Thus, the combination of SSG and IFN-α 2b was necessary to induce expression of perforin A by these innate immune cells.

Whereas NK cell activity is associated with innate immunity, CD8+ CTL is required for adaptive immunity. Sustained adaptive immunity depends upon the production of IL-2 by activated CD4+ T cells to sustain T-cell proliferation and the production of IFN-γ by activated macrophages to co-stimulate CD8+ CTL. As T_R cells inhibit the production of IL-2 by activated T cells [26], the reduction in T_R activity is desirable for an adequate antitumor response. In the current study, administration of low-dose and high-dose SSG alone yielded significantly lower percentages of T_R cells. However, IL-2 production by TCR-activated T cells was observed only in patients receiving high-dose SSG, and only after adding IFN-α 2b. Activation of T_R cells inhibits production of IL-2 by activated T cells [26]. Although we did not measure circulating levels of IFN-γ, we measured IL-12 produced by mDC following activation through the TLR. IL-12 is responsible for inducing IFN-γ by T cells and NK cells [25]. Unfortunately, SSG alone and in combination with IFN-α 2b failed to significantly augment the percentage of TLR-activated mDC that produced IL-12. This may account for the lack of IFN-γ production by T cells and the resultant lack of antitumor activity in our patients. Others reported increases in plasma levels of IFN-γ and in the percentage of CD4+ T cells that were capable of producing IFN-γ [27] as well as increased IFN-γ mRNA expression by alveolar macrophages following SSG administration [28] in mice.

This study was limited by the lack of a cohort that received IFN-α 2b prior to SSG, which would have permitted comparing IFN-α 2b and SSG as single agents, thereby helping to determine the optimal immune modulatory effect of these two drugs. This was not done because of limitations inherent in a phase I study.

In conclusion, SSG in combination with IFN-α 2b was well tolerated at 900 mg/m² and demonstrated immune modulation. There was an increase in the proportion of TLR7- and TLR8-activated pDC in patients receiving high-dose SSG that produced IFN-α. These data represent increased adaptive and innate immune responses following therapy with high-dose SSG in combination with IFN-α 2b.

Conflict of Interest

Declared none other than Sponsored Research Agreement with VioQuest Pharamceuticals, Inc.

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