

A phase II pilot trial investigating the efficacy and activity of single agent granulocyte macrophage colony-stimulating factor as maintenance approach in castration - resistant prostate cancer patients responding to chemotherapy

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ABSTRACT

Purpose: To investigate the toxicity and efficacy of GM-CSF in castration-resistant prostate cancer (CRPC) patients who maximized their response to systemic chemotherapy. **Materials and Methods:** CRPC patients who maximized their response to either docetaxel or mitoxantrone chemotherapy were eligible if they demonstrated adequate performance status, liver, kidney, and bone marrow function. Maximum response to chemotherapy was defined as either receiving at least 8 cycles of chemotherapy without radiographic or biochemical progression, receiving less than 8 cycles as long as the prostate-specific antigen (PSA) changes by less than 10%, or being off chemotherapy for less than 12 weeks without disease progression. Patients received GM-CSF at 250 mcg/m² subcutaneously for 14 days followed by 14 days of rest. GM-CSF was continued until disease progression. **Results:** Fifteen patients were enrolled of which all were evaluable for toxicity and 13 were evaluable for efficacy. Median age was 78 (range 66-96) and 93% of patients had a Gleason score \geq 7. Biochemically, 2 patients (15.3%) attained partial response (PR) and 4 (30.7%) had stable disease (SD). Median time to PSA progression was 6 months (range 4-12). Radiographically, 9 patients (69.2%) had SD that lasted a median of 6 months (range 2-10). With a median follow-up of 24 months from starting GM-CSF (range 2-38), 2 patients (13.3%) remain alive and well. Median OS from start of any chemotherapy was 21 months (range 10-44). GM-CSF was well-tolerated with minimal expected manageable toxicities. **Conclusions:** GM-CSF is active post-chemotherapy in CRPC patients. Further studies with GM-CSF in this setting are warranted.

Key words: Biologic therapy, castration-resistant, GM-CSF, hormone refractory, prostate cancer

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy in United States' men.^[1] Despite early detection and screening, many patients present with or develop metastases at some point during the course of their disease.^[2] Although 80-85% of patients will achieve temporary control and regression of their metastases with androgen deprivation therapy (ADT), almost all patients become resistant to

ADT developing a castration resistant state (CRPC).^[3] While recent advances in CRPC have been witnessed with the introduction of immunotherapy and other hormonal agents,^[4-6] symptomatic patients are generally treated with palliative systemic chemotherapy; generally

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docetaxel-based.^[7,8] Median survival for those treated with chemotherapy remains suboptimal at less than 20 months.^[9] Importantly, despite initial witnessed responses with chemotherapy; disease progression ensues within 6 months or less.^[10]

Several studies have suggested increased overexpression of Granulocyte macrophage colony-stimulating factor (GM-CSF) in human prostate cancer cell lines.^[11,12] Immunolocalization studies showed low level expression of GM-CSF alpha and beta subunits in normal prostate tissue; with substantial expression in benign prostatic hyperplasia and prominent expression in neoplastic prostate tissue.^[13] Furthermore, a phase II study using GM-CSF in 36 men with progressive disease after androgen deprivation and anti-androgen withdrawal demonstrated activity.^[14] GM-CSF was administered subcutaneously at a dose of 250 microgram/m² daily for 14 days of a 28-day treatment period. While Prostate Specific Antigen (PSA) responses were observed, PSA levels climbed during the off-therapy period of the study. Also, one patient had radiographic improvement on a bone scan. Other trials confirmed GM-CSF activity in CRPC.^[15]

We hypothesized that incorporating GM-CSF as a maintenance approach for CRPC patients who have maximized their response to systemic chemotherapy could delay disease progression and ultimately improve patients' outcome. Herein, we report the final results of this phase II pilot trial.

MATERIALS AND METHODS

Eligibility criteria

Eligible patients were those with known pathologic diagnosis of adenocarcinoma of the prostate who have maximized their response to systemic chemotherapy (docetaxel or mitoxantrone) given for the treatment of their CRPC. Maximum response to chemotherapy was defined as any of the following: *a*) patients receiving a minimum 8 cycles of chemotherapy for CRPC without evidence of disease progression but do not wish to continue chemotherapy, *b*) patients achieved their maximal response despite receiving less than 8 cycles of chemotherapy defined as a drop in PSA value by $\leq 10\%$ on two consecutive measurements without radiographic progression, *c*) patients who have completed their chemotherapy 12 weeks prior to enrollment and have not progressed since stopping chemotherapy. Castration levels of testosterone (< 50 ng/dl) and continuing ADT throughout were required. Patients must have had a PSA level ≥ 5 ng/dl and a life expectancy of at least 6 months with an Eastern Cooperative Oncology Group (ECOG)

performance status ≤ 1 . Adequate hematologic, renal, and liver function as evidenced by the following: white blood cell counts > 2000 , absolute neutrophil count > 1000 , Platelet count $> 100,000$, hemoglobin > 9.0 g/dl, Creatinine < 2 , total bilirubin $< 2x$ upper limit of normal, aspartate aminotransferase (AST) and Alanine Transaminase (ALT) $< 3x$ upper limit of normal were required. Patients were allowed to continue the use of intravenous bisphosphonates. Patients were excluded if they had known brain metastases, HIV positive status, and had a performance status ≥ 2 . Patients with prior exposure to more than one chemotherapy program are *not* excluded. Patients with other active malignancies (excluding non-melanoma skin cancers) were excluded. Prior malignancies were allowed as long as last treatment for such malignancies was over 5 years prior to enrollment. All patients signed a written informed consent. The study was approved by the Institutional Review Board and adhered to human protection guidelines per the declaration of Helsinki. The study was registered at www.clinicaltrials.gov (NCT 00274287)

Study design and treatment plan

Once enrolled, patients received GM-CSF at 250 ug/m² subcutaneously daily for 2 weeks followed by 2 weeks of rest. This program continued until disease progression, toxicity, investigator's discretion, or patient's withdrawal. After progression, patients were treated at the investigator's discretion. Toxicity was assessed every cycle (4 weeks) and response was evaluated every 2 cycles (8 weeks). Patients underwent bone scans and computed tomography of measurable disease areas every 2 cycles. Laboratory assessment included complete blood count, complete metabolic panel, and PSA every 2 cycles.

End points and Follow up

This trial was designed to investigate the efficacy and safety of GM-CSF when applied as a maintenance strategy in CRPC individuals who have maximized their response to systemic chemotherapy as defined above. The primary end point was assessing time to disease progression (TTP) defined as the time from starting chemotherapy until progressive disease (PD) radiographically and/or biochemically. Secondary end points included overall survival (OS), toxicity of GM-CSF, and time to next treatment (TTNT). Once off study, patients were followed every 3 months until death or 3 years whichever occurred first.

Dose modifications

For grades 1 and 2 toxicities, treatment was continued on schedule with appropriate implementation of supportive measures. GM-CSF was held for grade 3 toxicity until toxicity subsided to \leq grade 1 after which treatment was

resumed at the same dose. Missed doses were not replaced. Dose reduction in GM-CSF by 25% was applied only for grades 3 cardiac or neurologic events. If grade 3 toxicities did not resolve within 4 weeks of experiencing the event, the patient was taken off study. Any patient who experienced grade 4 adverse events was taken off trial

Assessment of response

Radiographic disease

Complete response (CR) was defined as disappearance of all measurable lesions including bone lesions, no new lesions, and no disease-related pain. Patients who still had bone lesions but had resolution of their visceral metastases were classified as having a partial response (PR). Any response was confirmed by a repeat assessment within 4 weeks. PR was defined as more than 30% decrease in the sum of longest diameter of measurable lesions compared to baseline. Stable disease (SD) was defined when the lesions did not meet criteria for PR or progressive disease (PD). PD was defined as more than 20% increase in the sum of longest diameter of measurable lesions compared to baseline, and/or evidence of new lesions on imaging studies. The appearance of 2 or more new bony lesions on a bone scan, development of cord compression, and pathologic fractures constituted PD.

Biochemical assessment

Serum PSA was measured every 8 weeks while patients received GM-CSF. For patients with measurable disease, PSA progression in the absence of radiographic disease progression was not considered PD and patients were allowed to continue on GM-CSF. For patients with a PSA ≥ 20 ng/dl, biochemical CR was defined as a PSA < 4 ng/dl confirmed on a repeat measurement 3 weeks after. Biochemical PR was defined as a PSA that decreases by 50% and maintained for at least 3 weeks by confirmatory measurement. Biochemical SD was defined as PSA that increased by less than 25% or decreased by less than 50%. Patients with stable PSA or any PSA response were continued on study. Biochemical PD was defined as an increase of at least 25% confirmed 3 weeks after. For patients with a PSA < 20 ng/dl, PSA progression was defined as an increase by 100% or more. Importantly, patients who have a mixed response (meeting a criteria for response for radiographically measurable but having PSA progression) were considered stable and were reassessed 8 weeks later as long as they were tolerating therapy without adverse events that warrant stopping treatment.

Statistical considerations

This was a phase II open label pilot study investigating GM-CSF maintenance approach in patient maximizing their response to chemotherapy given for their CRPC.

Since this was a pilot study, a sample size of 15-25 patients depending on funding was viewed adequate for the purpose of obtaining preliminary efficacy information. The sample size was not based on any statistical justifications since there was no hypothesis testing. Primary and secondary efficacy endpoints were analyzed and presented for all evaluable patients.

RESULTS

Patients characteristics

Due to lack of funding, only fifteen patients were enrolled of which 13 were evaluable (1 patient withdrew consent and another was non-complaint with study follow-up requirements). Median age was 78 (range 66-96) and 93% of patients had a Gleason score ≥ 7 . Seven patients (47%) were diagnosed with metastatic disease at presentation. Median time from initial diagnosis to starting GM-CSF on study was 71 months (range 19-145). Table 1 summarizes baseline characteristics of all enrolled patients

Efficacy

Of 15 enrolled patients, 2 were in-evaluable and were excluded from efficacy assessment. When analyzing PSA response, 2 patients (15.3%) attained a PR, 4 (30.7%) had SD, and 7 (53.8%) had PD. Median time to PSA progression was 6 months (range 4-12). The biochemical PR patients had a reduction in their serum PSA of 70% and 84% respectively. Looking at radiographic response, 9 patients (69.2%) had SD that lasted a median of 6 months (range 2-10) and 4 patients (30.8%) had PD. Median time to any progression (PSA or imaging) was 6 months (range 2-12) from start of GM-

Table 1: Baseline patients' characteristics of all enrolled patients

Number of patients	15 (100%)
Median age	78 (range 66-96)
Race	14 (93.3%) White 1 (6.7%) Asian
Gleason ≥ 7	14 (93%)
Median time from diagnosis to GM-CSF	71 months (range 19-145)
Median number of prior therapies [^]	2 (range 1-3)
Median PSA	51.7 (range 0.1-566)
Median alkphos	97 (31-245)
Prior initial therapy	5 (33.3%) RT 3 (20%) RP 7 (46.7%) ADT
Site of metastases	7 (46.7%) bone 7 (46.7%) bone and visceral disease 1 (6.6%) Visceral

RT=Radiotherapy, RP=Radical prostatectomy, ADT=Androgen deprivation therapy, GM-CSF= Granulocyte macrophage colony-stimulating factor already provided, not sure what I am being asked to do!!, PSA=Prostatic specific antigen, Alkphos=Alkaline phosphatase, ^ Excluding initial therapy and ADT

CSF. TTP from start of any chemotherapy was 11 months (range 9-21). With a median follow-up of 24 months from starting GM-CSF (range 2-38), 2 patients (13.3%) remain alive and well. Of importance, median OS from start of any chemotherapy was 21 months (range 10-44) [Table 2].

Toxicity

GM-CSF was well-tolerated. Only one patient was taken off study after 6 cycles per his choice due to grade 2 injection site reaction. Six patients (40%) were hospitalized during the study period but although two events only were considered related to GM-CSF (fatigue and dehydration). Two patients with known cardiac history developed atrial fibrillation and myocardial ischemia as adverse events respectively, but neither was considered secondary to GM-CSF. Another patient developed bowel obstruction due to umbilical and ventral hernias. One patient developed central line infection requiring intravenous antibiotics. Hematologic toxicities were minimal with only one patient developing

grade 3 thrombocytopenia and another having grade 3 hypoalbuminemia; neither considered related to GM-CSF [Table 3].

DISCUSSION

There is no known standard approach to CRPC patients who maximize their response to systemic chemotherapy. Traditionally, patients are observed until disease progression. Median time to disease progression after docetaxel-based chemotherapy is 7 months and median duration of pain relief after docetaxel is less than 4 months.^[8] Accordingly, strategies to improve on these modest outcomes are needed. In this pilot study, we demonstrate that GM-CSF is active in docetaxel or mitoxantrone-treated patients. In fact, GM-CSF improves on observed responses with either chemotherapy drug with 40% of patients having SD or better biochemically. When assessing disease response radiographically, only SD was observed lasting a median of 6 months. Also, median time to any progression whether by PSA or imaging was 6 months. Importantly, Median OS was 21 months from the start of any chemotherapy which compares favorably with median OS of 19 months using docetaxel alone.^[9] TTP from initial chemotherapy exposure in our study was 11 months which appears superior to what has been historically reported with chemotherapy alone. GM-CSF was well-tolerated without serious adverse events that were drug-related. Most adverse events were expected and manageable.

Based on initial observations demonstrating activity of GM-CSF in prostate cancer,^[14] Dreicer *et al*, used GM-CSF in 16 patients with advanced prostate cancer; 7 of whom were hormonally naïve and 9 were androgen-independent.^[15] A dose of 250 mcg thrice weekly for 6 months was used while PSA measurements took place every 2 weeks. No patient achieved an objective response; however 6 patients demonstrated a 10-15% decline in their

Table 2: Efficacy of granulocyte macrophage colony-stimulating factor after chemotherapy in the enrolled patients

Total patients	15 (100%)
Evaluable patients	13 (86.6%)
Immediate past chemotherapy before GM-CSF	12 (80%) docetaxel 3 (20%) mitoxantrone
PSA PR	2 (15.3%)
PSA SD	4 (30.7%)
PSA PD	7 (53.8%)
Radiographic SD	9 (69.2%)
Radiographic PD	4 (30.8%)
Median TTP from GM-CSF	6 months (2-12)
Median TTP from chemotherapy	11 months (9-21)
Median number of GM-CSF cycles	6 (2-12)
Median OS from start of GM-CSF	12 (2-38)
Median OS from start of chemotherapy	21 months (10-44)

GM-CSF=Granulocyte-macrophage colony stimulating factor, PSA=Prostatic specific antigen, PR=Partial response, PD=Progressive disease, SD=Stable disease, OS=Overall survival, TTP=Time to progression

Table 3: Toxicities on granulocyte macrophage colony-stimulating factor (15 evaluable patients for toxicity)

Grade 3 and/or 4 laboratory	Grade 2 or less laboratory	Grade 3 and/or 4 non-hematologic	Grade 2 or less non-hematologic
Elevated alkphos 1	Low albumin 4 (26.6)	Weakness 2 (13.3)	Fatigue 2 (13.3)
Thrombocytopenia 1	Hypercalcemia 1(6.6)	Dehydration 1(6.6)	Weakness 4 (26.6)
Low albumin 1	Hyponatremia 3 (20)		Blurry vision 3 (20)
Hypokalemia 1	Thrombocytopenia 2 (13.3)		Weight loss 4 (26.6)
6.6% each	Hypocalcemia 1(6.6)		Vomiting 2 (13.3)
			Nausea 1 (6.6)
			Insomnia 1 (6.6)
			Mouth dryness 1(6.6)
			Dysguisa 1(6.6)
			Reflux 2 (13.3)
			HTN 1(6.6)
			Diarrhea 1(6.6)

HTN=hypertension, Figures in parentheses are in percentage.

baseline PSA which was maintained during the entire treatment period. Only 1 grade 3 event which was not treatment-related was witnessed. Other studies focused on combining GM-CSF with other agents. A phase II trial combined GM-CSF with thalidomide in CRPC. GM-CSF was given subcutaneously at 250 mcg thrice weekly with escalating doses of thalidomide up to 200 mg/day.^[16] Of 22 enrolled patients, 5 had $\geq 50\%$ decline in PSA from baseline. Therapy was well tolerated with the majority of patients experiencing only one event. Combining GM-CSF with an anti-HER-2 protein in HER-2 over-expressing CRPC proved feasible, improves pain, and reduces PSA velocity.^[17] The immunomodulatory effects of GM-CSF have led to incorporating this agent in vaccine studies with variable results. An open-label, multicenter, dose-escalation study evaluated multiple dose levels of immunotherapy in CRPC patients. The immunotherapy consisted of 2 allogeneic prostate-carcinoma cell lines modified to secrete GM-CSF.^[18] Eighty men were treated with injection-site erythema being the most noted adverse event. Median survival time was 35 months in the high-dose group and PSA stabilization occurred in 15 (19%) patients while $>50\%$ decline in PSA was seen in 1 patient. GM-CSF has also been combined with CTL-associated antigen 4 (CTLA4) which is a co-stimulatory molecule expressed on activated T cells that delivers an inhibitory signal to T cells. Accordingly, blocking CTLA4 has been shown to enhance anti-tumor immunity and has shown activity in prostate cancer.^[19] Fong *et al.*, combined ipilimumab (anti-CTLA4) with GM-CSF in 24 metastatic CRPC patients.^[20] This immunotherapy combination proved effective inducing the expansion not only of activated effector CD8 T cells *in vivo* but also of T cells that are specific for known tumor-associated antigens from the endogenous immune repertoire. The ability of GM-CSF to modulate the immune system of CRPC patients led to incorporating this agent in designing sipuleucel-T immunotherapy that has demonstrated improvement in OS when compared to placebo in patients with asymptomatic or minimally symptomatic CRPC.^[5]

While chemotherapy has changed the natural history of CRPC by demonstrating improvement in OS, toxicities of chemotherapy preclude continued administration making the identification of non-chemotherapy approaches critical. Such approaches are usually based on basic understanding of mechanisms by which prostate cancer becomes castration-resistant.^[3,21] Immune deregulation has been hypothesized as an important pathway by which the disease becomes refractory to traditional therapies. Accordingly, exploiting this pathway was a reasonable approach in an attempt to maximize on a response already observed in patients receiving chemotherapy for their CRPC.

In summary, we demonstrate that GM-CSF can be given safely after chemotherapy and in some patients, biochemical responses are augmented. Furthermore, OS might be potentially improved when adding GM-CSF after chemotherapy and TTP is likely enhanced. A prospective study comparing docetaxel and prednisone to the same combination with GM-CSF is warranted.

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