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Regression of metastatic cancer and abscopal effects following *in situ* vaccination by cryosurgical tumor cell lysis and intratumoral immunotherapy: A case series

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ABSTRACT

Purpose: To evaluate the efficacy and safety of a novel *in situ* cancer vaccination method for the treatment of aggressive solid tumors, with an initial focus on metastatic prostate cancer (mPCa).
Procedure: 27 consecutive patients with metastatic cancers (21 with mPCa and 6 with other cancers), were treated by *in situ* cryosurgical lysis of tumor tissue followed by injection of ipilimumab, pembrolizumab or nivolumab, and sargramostim directly into the zone of lysis. This was followed by 30 daily SC injections of sargramostim. Patients received 1 to 3 cycles of the above therapy at intervals of ≥ 1 month. Responses to therapy were assessed by RECIST v.1.1 and for patients with mPCa, serum PSA levels. This IRB-approved study, Shulman IRB Protocol #00027107, is a retrospective analysis (with prospective follow-up) of the practice of medicine of two physicians. All patients signed informed consent.
Results: 21 patients with progressive mPCa and 6 with other metastatic cancers (2 bladder, 1 pancreatic, 1 colon, 1 melanoma, and 1 unknown) were treated. RECIST responses for 3 patients (all with mPCa) could not be evaluated due to a lack of follow-up imaging. Among the remaining 24 patients, CRs were seen in 9 (38%) patients and a PR in 1 (4%), for an ORR of 42%. SD was seen in 8 (33%) patients, and progression was seen in 6 (25%).
Among the 18 evaluable mPCa patients, there were 9 (50%) CRs and no PRs, for an ORR of 50%. 6 (33%) patients showed SD, and 3 (17%) progressed. 13/21 (62%) of patients had post-therapy PSA reductions of > 50%.
12 mPCa patients were ADT-naïve (10 evaluable by RECIST) and there were 9 patients that were ADT-experienced (8 evaluable by RECIST), and positive responses were seen in both groups, with ORRs of 60% and 38%, respectively, and PSA reductions of > 50% in 75% and 44% of patients, respectively.
These antitumor responses have been durable in many patients, with CRs to date ranging from 1 to over 4.5 years post-treatment. Encouragingly, this durability of response was observed both in ADT-naïve patients and in those with mCRPC.
Therapy was well tolerated, with AEs in 19/27 (70%) of patients. 24 grade 1-2 AEs were seen in 19 (70%) patients, and 8 grade 3-4 AEs were seen in 5 (19%) patients. Notably, AEs included liver enzyme elevations, hyperthyroidism and hypothyroidism, all of which are associated with autoimmune responses to immunotherapy. One death that was possibly treatment-related, 4 disease-related deaths, and 2 unrelated deaths occurred.
Conclusions: This report describes a novel therapeutic modality utilizing local cryosurgical cell lysis and intratumorally-delivered immunotherapy to treat metastatic prostate cancer and other aggressive solid tumor cancers. Its combination of striking efficacy and good tolerability supports additional formal clinical studies.

OBJECTIVES

- To evaluate the safety, tolerability and clinical benefit of a novel *in situ* cancer vaccination method utilizing cryosurgical cell lysis coupled with intratumoral immunotherapy
- Eliciting immunogenic tumor cell death by freezing a portion of a tumor
- Injecting the three immunotherapeutic drugs into the zone of lysis
  - GM-CSF, to promote differentiation of hematopoietic progenitor cells to antigen presenting cells and to recruit DCs to the sites of treatment and antigen presentation
  - Relieving CTLA-4-mediated downregulation of T cell activation and facilitating clearance of circulating Tregs and myeloid-derived suppressor cells
  - Inhibiting PD-1 to stimulate tumor cell killing by activated T cells, locally and ultimately, in distant metastases

METHODS

ClinicalTrials.gov ID number: NCT03695835
In the course of a medical practice between April 2015 and December 2019

27 advanced metastatic cancers (21 with prostate cancer and 6 with other cancers)

→ **1 to 3 cycles of *in situ* cryosurgical cell lysis at intervals of ≥ 1 month**
+
injection of ipilimumab, pembrolizumab or nivolumab, and sargramostim into the zone of lysis
+
30 daily SC injections of sargramostim

→
- Retrospective analysis (with prospective follow-up) of the practice of medicine of two physicians
- Responses to therapy were assessed by RECIST v.1.1 and for patients with mPCa, serum PSA levels

RESULTS

Table 1. Patient Characteristics

Variable	N (%)
Age at first treatment, median (range) y	65.5 (49-81)
Metastatic cancer ranging from treatment-naive to heavily pretreated (ADT, radiation, chemotherapy and radical prostatectomy)	
Prostate	21 (78)
Colon	1 (4)
Bladder	2 (7)
Pancreas	1 (4)
Melanoma	1 (4)
Unknown	1 (4)
ADT	
Naïve	12 (44)
Experienced	9 (33)
# of treatment cycles per patient	
1	10 (37)
2	5 (19)
3	12 (44)

Table 2. Summary of Adverse Events* (All Cancers)

Grade	# of AEs	# of Patients	% of Patients
1	8	8	30
2	16	14	52
3	3	3	11
4	5	2	7
5	1	1	4

*National Cancer Institute Common Terminology Criteria for Adverse Events v5.0

Table 3. Summary of Overall Response in All Evaluable Patients (per RECIST v1.1)

Response	N	Total*	%
Objective Response	10	24	42
Complete Responses	9	24	38
Partial Response	1	24	4
Stable Disease	8	24	33
Progression	6	24	25

RECIST, Response Evaluation Criteria in Solid Tumors.
*RECIST responses for 3 patients (all with prostate cancer [PCa]) could not be evaluated due to a lack of follow-up imaging

Table 4. Summary of Overall Response in Evaluable PCa Patients (per RECIST v1.1)

Response	N	Total*	%
Objective Response	9	18	50
Complete Responses	9	18	50
Partial Response	0	18	0
Stable Disease	6	18	33
Progression	3	18	17
PSA decline of > 50%	13	21	62

RECIST, Response Evaluation Criteria in Solid Tumors.
*RECIST responses for 3 patients (all with prostate cancer) could not be evaluated due to a lack of follow-up imaging

Table 5. Summary of Response for ADT-Naïve PCa Patients

Response	N	Total*	%
Objective Response	6	10	60
Complete Responses	6	10	60
Partial Response	0	10	0
Stable Disease	3	10	30
Progression	1	10	10
PSA Response > 50%	9	12	75

RECIST, Response Evaluation Criteria in Solid Tumors.
*RECIST responses for 3 patients (all with PCa) could not be evaluated due to a lack of follow-up imaging

Table 6. Summary of Response for ADT-Experienced PCa Patients

Response	N	Total*	%
Objective Response	3	8	38
Complete Responses	3	8	38
Partial Response	0	8	0
Stable Disease	3	8	38
Progression	2	8	25
PSA Response > 50%	4	9	44

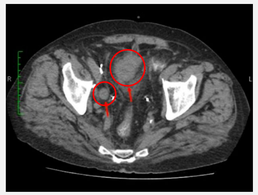
RECIST, Response Evaluation Criteria in Solid Tumors.
*RECIST responses for 3 patients (all with PCa) could not be evaluated due to a lack of follow-up imaging

Figure 1. **Patient #1**

A.

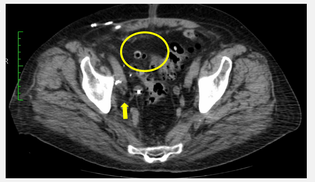
Summary treatment history	Diagnosed in 1994; patient underwent radical prostatectomy, radiation, investigational drug, luprolide, flutamide, histrelin, abiraterone, prednisone, docetaxel, cabizitaxel
Cancer	Metastatic prostate
Location of Mets	Pelvis, bladder, abdominal & pelvic nodes, rectum
ECOG	Grade 3
# of treatment cycles	1
RECIST score	CR (pathologically confirmed)

B.



Pre-Treatment CT Scan 1/16/2015. CT scan of the pelvis prior to treatment shows an enlarged obturator lymph node (small red circle) measuring 2 cm and a pelvic mass of locally recurrent prostate cancer after a radical prostatectomy (large red circle) measuring 4 cm x 4 cm.

C.



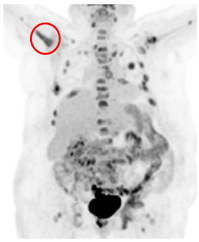
Post-Treatment CT Scan 10/21/2019. A recent CT scan confirms that more than 4 years later the area of the previous mass is normal (yellow circle) and the lymph node still is normal in size (yellow arrow).

Figure 2. **Patient #19**

2A.

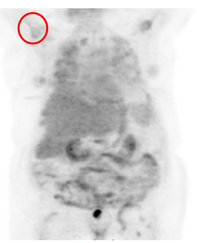
Summary treatment history	No prior treatment; previous medical history of diabetes mellitus and obesity
Cancer	Metastatic cancer of unknown etiology
Location of Mets	Lung, bone, mediastinal nodes
ECOG	Grade 4
# of treatment cycles	1
RECIST score	SD (tumors not measurable)

2B.



Pre-Treatment PET Scan 8/25/2017. Composite view of scan above. Patient's tumor burden was enormous with bone lesions too numerous to count (red circle highlights uptake in the patient's right humerus).

2C.



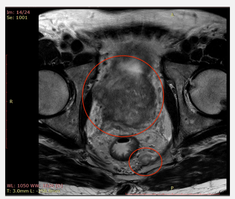
Post-Treatment PET Scan 11/1/2017. Post treatment scan shows virtually all visible lesions have markedly decreased in intensity (note the change in the humerus).

Figure 3. **Patient #27**

3A.

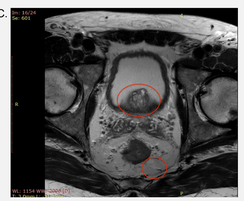
Summary treatment history	No prior treatment
Cancer	Metastatic prostate
Location of Mets	Multiple pelvic & iliac, retroperitoneal nodes, left femur head, L4 vertebra, appendicular & axial skeleton
ECOG	Grade 0
# of treatment cycles	2
RECIST score	CR

3B.



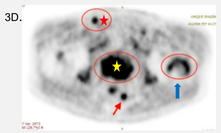
Pre-Treatment MRI Pelvis 11/7/2018. Axial view shows the tumor in Figure 1 replacing the normal prostate (circle). The bladder is pushed anteriorly and the seminal vesicles are infiltrated and not discernable.

3C.



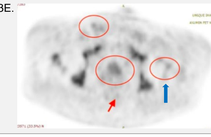
Post-Treatment MRI Pelvis 1/31/2019. Axial view shows the prostate has returned to a normal size (circle) with a small BPH nodule visible. The bladder has returned to its normal position and the seminal vesicles are now visible.

3D.



Pre-Treatment Axumin Scan 11/8/2018. This level of the Axumin scan shows multiple areas of abnormal uptake in various structures. The nodal mets are represented by the red arrow and the red star. The star is uptake in the prostate mass and the blue arrow is uptake in the lesion in the left femoral neck.

3E.



Post-Treatment Axumin Scan 1/31/2019. The multiple areas of abnormal uptake in have all resolved. The remaining uptake in the area of the left femoral neck is the normal background uptake seen in normal bone marrow (blue arrow).

CONCLUSIONS

- These data provide proof of concept that this approach is capable of yielding a favorable mix of efficacy and tolerability against cancers that have thus far eluded effective control by other means.
- These data support additional formal clinical studies.

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