The role of immune modulation and anti-inflammatory agents in the management of prostate cancer: A case report of six patients

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Abstract. Cancer is associated with chronic inflammation and disruption to normal immune function. As such, the ability to thrive in a chronically inflamed microenvironment is regarded as a hallmark of cancer. Therefore, targeting inflammation and/or correction of aberrant immunity has been a therapeutic aim. The aim of the present study was to describe the use of a novel immunotherapy, called IMM-101, which is a naturally occurring, heat-killed whole cell mycobacterium, used in combination with conventional treatments in patients with prostate cancer. The present study analysed and presented data from six patients diagnosed with prostate cancer, some of whom have metastatic disease. Treatment regimens included the use of IMM-101, the correction of vitamin D3 levels, and combination with other agents that have anti-inflammatory and immune-modulatory abilities, such as bromelain and low-dose naltrexone (LDN). Clinical responses were detected in the patients when IMM-101 was commenced and further improvements were seen when an anti-inflammatory agent was used in unison. Combination therapy quickly led to a reduction in prostate-specific antigen levels, and stabilisation of disease was often achieved as indicated by repeat MRI and PET scans. Few side effects of any kind were observed when using these combination treatments. In conclusion, IMM-101 treatment alongside an anti-inflammatory agent, such as bromelain and/or LDN, may be considered an active and safe drug combination, and is a regimen that should be considered for treating patients with prostate cancer.

Introduction

The role of immunotherapy in patients with prostate cancer has been acknowledged for several years including the fact that the first vaccine treatment approved for humans in the form of sipuleucel-T was for prostate cancer (PC) and not melanoma (1,2). Nevertheless, the checkpoint inhibitors (CPIs) such as pembrolizumab and nivolumab have not had the impact in PC seen in other solid tumours such as melanoma and lung cancer (3). In an attempt to optimise a cell-based vaccine for prostate cancer a number of different strains of mycobacteria were investigated, and it was soon noted that *Mycobacterium bovis* [bacillus Calmette-Guérin (BCG)] and heat-killed *Mycobacterium sp.* were the best adjuvants (4). Indeed, *Mycobacterium vaccae* (*M. vaccae*) alone had an impact on prostate specific antigen (PSA) levels in a small clinical trial (5).

Immunotherapy has had a dramatic impact on a large number of solid tumours including melanoma, lung cancer, head and neck cancer and lymphoma amongst others, but so far, these agents, typified by the CPIs have had little impact on PC cancer (3). This is perhaps surprising given that a vaccine for the treatment of advanced PC was approved in 2010 (1). Moreover, there is historical evidence of activity in a number of different vaccine approaches having a clinical effect, including *M. vaccae* (4), whole cell-based vaccine with or without genetic modification (5,6) as well as vaccines with multiple co-stimulatory factors.

M. vaccae has previously been reported as having an effect on PSA levels when used alone in a small clinical study. It was mainly used in melanoma and lung cancer studies before being dropped by the pharmaceutical company SR Pharma. However, the survival of the melanoma patients treated with *M. vaccae* was sufficiently good to lead to its resurrection by a new company called Immodulon Therapeutics. Further research showed that *Mycobacterium obuense* (*M. obuense*) was a better immunogen/immune modulator and was much easier to produce to good manufacturing practice (GMP). It is now known as IMM-101, and has been associated with increased survival in a randomised trial in advanced pancreatic patients (7).

IMM-101 is currently being assessed as a novel immune-therapy employed as a general adjunct to chemotherapy. Like immuno-oncology therapies, it is based on the evidence that the host immune system, when appropriately modulated, is able to generate protective responses against malignant cells. As a result of its ongoing success in melanoma and pancreatic cancer, a number of patients with PC requested access to IMM-101 on a named patient program. Additional research has shown that low levels of vitamin D3 are an

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issue in PC as well as several other tumour types (8), and so patients also received vitamin D3 supplementation to correct these levels. Furthermore, the role of anti-inflammatories has been reported in several studies with a benefit for daily aspirin alone (9). Other agents have been identified as having significant anti-inflammatory effects such as bromelain (10) and naltrexone in low doses (LDN) (11). LDN has been identified by our group as being a significant TLR-9 antagonist (12) and an agent with anticancer properties (13). Neither bromelain and naltrexone have been reported as having any gastro-intestinal side-effects, and so in some instances, these and other anti-inflammatory agents were used. Every patient in this study signed an informed consent allowing anonymous use of their data.

Case report

Patient 1: Significant response of bone metastases following the addition of IMM-101 and Zometa to standard hormone treatment. A 61-year-old man was diagnosed with PC following biopsy and magnetic resonance imaging (MRI) staging for an elevated PSA in 2008. He commenced on bicalutamide with a fall in PSA from 4.2 to 1.4. In 2010, he presented with severe hip pain, and scans confirmed multiple bone metastatic lesions in his pelvis. He was commenced on goserelin with little change in his PSA. He was subsequently referred for *M. vaccae*, having become aware of a clinical trial in 2005 (5), and this was commenced along with zoledronic acid as he had bone pain. His PSA fell to 0.39 within six-months, and a repeat scan showed resolution of all bone metastases. One-year later, he was treated with radiotherapy (RT) to the primary and lymph nodes (35 sessions). He subsequently became stable and well on three monthly injections of *M. vaccae*. He stopped all hormone treatment in 2013. In 2016, the patients switched over to IMM-101 with the continued use of three-monthly zoledronic acid.

The patient had a relapse in two lymph nodes and one seminal vesicle, and was treated with Cyberknife in 2017. Currently, he remains on IMM-101, and a small rise in his PSA level resulted in the recommencement of combined androgen blockade. He remains otherwise well nine years later, after starting immunotherapy for metastases including bone deposits.

Patient 2: Six years stable disease following IMM-101 to avoid combined androgen blockade (CAB) therapy because of side-effects. A 56-year-old man presented in 2004 with a PSA of 6.0 on screening as he had a strong family history of PC. He had a radical prostatectomy for a Gleeson 3+4 bilaterally in 6/10 cores. There was extracapsular extension and invasion of the left seminal vesicle. He had RT to the prostate bed (66 Gy in 33 fractions) without androgen deprivation. Since his PSA has been slowly increasing, he was not keen to commence hormone treatment and was referred by his surgeon for consideration of IMM-101 in order to delay the inevitable need for CAB. He was on aspirin, and was already aware of the importance of vitamin D3 correction and anti-inflammatory agents. He commenced on IMM-101, which slowed his PSA doubling time, and his condition was monitored by MRI of the pelvis every six months. There was no evidence of any disease progression for nearly six years before there was evidence of local progression and at which time he commenced CAB. He was delighted to have had nearly six years of good quality of life without the side-effects of hormone therapy.

Patient 3: Five years stable disease following IMM-101 to avoid combined androgen blockade (CAB) therapy because of side-effects. A 69-year-old man presented with symptoms of a prostate problem and an elevated PSA in 2010. He underwent a radical prostatectomy for a Gleason 4+3 with bilateral peri-prostate invasion followed by intensity-modulated radiation therapy (IMRT) under six months of endocrine therapy. In spite of this, his PSA started to rise and he requested to receive IMM-101 under the named patient programme in 2013. His low vitamin D3 level was corrected and he was put on bromelain. His PSA continued to rise slowly and he was monitored by MRI and PET. In late 2017, PET scans showed positive para-aortic nodes. He was considered for further RT, but thought to be more appropriate for CAB treatment. He had five years of good quality of life and avoided the side-effects of CAB treatment during this time.

Patient 4: Three years stable disease on IMM-101 and LDN, without hormone treatment. Complete response to chemotherapy for LN progression, and further stable disease five years on. A 61-year-old man presented with prostatic symptoms and a rising PSA. He had a radical prostatectomy for a T2b Gleason 4+3 cancer, which was upgraded to 4+5 following biopsy of excised samples. Both lobes showed extra-prostatic extensions with tumour invading the base of both vesicles. He then had hormone treatment plus IMRT. Following cessation of hormone treatment, the patients wished to discuss alternative treatments, and as a consequence, in 2014 he was commenced on the IMM-101 programme, which also included LDN and correction of vitamin D3 levels. The patient had a slowly rising PSA with negative scans until late 2017 when he developed a new node, but remained negative for bone involvement. He was diagnosed as having aggressive progression by his oncologist and commenced on docetaxel. He had a dramatic response on MRI scans and PSA, which remains nearly undetectable 5-years on, and remains well on IMM-101 and LDN.

Patient 5: Nine-year survival in patient with aggressive disease and multiple bone metastases on presentation. Treated with IMM-101 and LDN. A 61-year-old medical physician with prostate cancer (Gleason 4+4) following investigation for bone pain and an elevated PSA was initially treated with goserelin. He requested access to the IMM-101 program after his PSA started rising after three years of stability and after conducting his own research of the literature. There was no response to bicalutamide, but there was a significant 53% fall in PSA since commencing IMM-101 (from 5.5 to 2.6). He also commenced LDN for its anti-inflammatory and immune-modulatory properties, and was stable clinically for two years when his PSA rose to 40.

The patient responded to the addition of abiraterone with a PSA of 1.5. In spite of progressive bone disease that was

Table I. Summary of six cases using IMM-101 and another anti-inflammatory agent in patients with prostate cancer.

Case	IMM-101 partner	Comments
1	Zoledronic acid	No response to single-agent goserelin. Fall in PSA within 6 months of treatment. Repeat scans showed resolution of bone metastases.
2	Aspirin	Treatment slowed PSA doubling time, MRI scanning q6m showed no evidence of disease progression.
3	Bromelain	Continued rise in PSA despite IMRT and endocrine therapy. Treatment slowed PSA doubling time and extended life.
4	LDN	Continued rise in PSA despite IMRT and endocrine therapy. Treatment resulted in a stable PSA and no disease on MRI.
5	LDN	No response to bicalutamide. Significant fall in PSA on commencement of treatment. Clinically stable for 2 years.
6	Aspirin, bromelain, LDN	Poor response to RT and bicalutamide. Combination treatment led to reduction in PSA and stable disease.

PSA, prostate-specific antigen; MRI, magnetic resonance imaging; IMRT, intensity modulated radiotherapy; LDN, low-dose naltrexone; RT, radiotherapy.

treated with radium-223 (6 cycles) and local RT, he remained extremely well and continued working as a physician. He had a further response to docetaxel and then subsequently to cabazitaxel, before having a rapid deterioration and dying nine years after presenting with a high-grade Gleason score and multiple bone metastases.

Patient 6: Five years stable disease with IMM-101 and LDN, without hormone treatment. A 62-year-old commercial aviator who was investigated for a rising PSA in 2007 and was found to have a Gleason score of 3+4+7 and T2(c). He underwent a radical prostatectomy and his pathology showed T3(b) disease with seminal vesicle invasion. The treatment regimen consisted of RT and bicalutamide. In spite of this, his PSA doubling time was 9 months. Further analyses showed low levels of vitamin D3 that was subsequently corrected, and he went on aspirin and bromelain. His own research led him to request IMM-101 on a named patient basis in early 2012. In spite of this, his PSA did not decline and he commenced on LDN, which had been noted previously to synergise with IMM-101 in patients with for melanoma. This combination quickly led to a reduction in his PSA level. He was stable on MRI and positron emission tomography (PET) scans until 2015 when he developed retroperitoneal lymphadenopathy. He was not thought suitable for Cyberknife, and was commenced on enzalutamide, which had an immediate effect on his PSA level. He remained well-controlled on this regime, and remained an active pilot until 2017 when he developed severe heart failure and an abdominal malignancy not related to his prostate cancer.

Discussion

Our *in vitro* studies have shown IMM-101 exhibited potent immune-modulatory properties that were anti-cancer in nature. These effects were seen when the agent was used alone and in combination with other immune-acting agents. Indeed, we have previously reported agents such as zoledronic acid (14) and LDN (13) can support tumour killing in these pre-clinical models. IMM-101 has been shown to be as safe and well tolerated when combined with standard chemotherapy, and the possible clinical benefit seen in a randomised trial (7) in another cancer type warrants further studies in a wider range of cancers. The only side effects seen in this cohort of patients to using IMM-101 was some redness/inflammation at the site of injection. Strangely enough, some patients reported immunity from viral infections, especially influenza. There were no adverse effects of using LDN in these patients discussed. However, the clinical experience of one of the authors has shown side effects are very rare for LDN. The usual ones are headaches and/or diarrhoea, and tended to occur post-surgery, and likely to be a consequence of interactions with opioids given as part of the pain management.

The fact that we have been able to document in the current case report, improvements in a few patients strongly supports further studies of IMM-101 combined with novel anti-inflammatory agents such as LDN and bromelain in PC patients who have responded sub-optimally to standard treatments (Table I). In some cases, the standard treatments had begun to fail. It is important to reiterate that this collection of individual case studies requires clinical trials to examine more completely the benefit of including IMM-101 in treatment regimens over those not using it.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

The study was conceived by AGD and contained cases belonging to him. AGD and WML confirm the authenticity of all the raw data. The report was written by WML and AGD. The data were analysed, examined and assessed by AGD and WML. Interpretation of the data and studies were performed by AGD and WML. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

All patients have provided written informed consent for publication.

Competing interests

AGD is a named inventor on a patent related to the use of LDN as a potential cancer therapy: Treatment of cancer with naltrexone; #9895438; date filed: May 12, 2015; date issued: February 20, 2018. AGD and WML are named inventors on a patent related to the use of LDN as a potential cancer therapy: Priming of cancer cells with low dose naltrexone; #11065245; date filed: June 9, 2015; date issued: July 20, 2021.

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