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Review Article

Dendritic cells pulsed with prostate-specific membrane antigen in metastatic castration-resistant prostate cancer patients: a systematic review and meta-analysis

Mohammad Mohammadzadeh [a], Masoud Shirmohammadi [b], Morteza Ghojazadeh [c, d], Leila Nikniaz [e], Mortaza Raeisi [f], Seyed Ali Mousavi Aghdas [g, *]

[a] Department of Radiology-Radiotherapy-Nuclear Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Gastroenterology, Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Iranian Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[d] RDCC, Medical faculty, Tabriz university of medical sciences, Tabriz, Iran
[e] Tabriz Health services management research center, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Hematology & Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[g] Students' Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Background: Dendritic cells (DCs) are used in many malignancies as vaccines to induce immunity against specific cancer antigens. The role of DCs in metastatic castration-resistant prostate cancer (mCRPC) is not determined. In this study, the proportion of mCRPC patients with clinically significant response to targeted therapy by DCs pulsed with prostate-specific membrane antigen was evaluated, and the possible adverse effects of this modality were investigated.

Methods: Major databases were searched up to Feb 2017, to identify studies in which the antitumor efficacy of DCs pulsed with the extracellular portion of PSMA was studied for the treatment of mCRPC. Data were collected by two reviewers and analyzed using Comprehensive Meta-Analysis software, version 2.0.

Findings: Our study consisted of 6 nonrandomized prospective (cohort) trials, overall reporting on 153 mCRPC patients. The event rate that is the representative of fraction of patients showing antitumor response was 0.43 (95% confidence interval = 0.355–0.512; $P = 0.097$). No significant between-study heterogeneity or inconsistency was detected ($I^2 = 5.47$; $Q = 5$; $P = 0.382$). Our study failed to demonstrate a significant therapeutic efficacy for DCs in mCRPC. However, no significant adverse effects were seen.

1. Introduction

Prostate cancer (PC) is the most commonly diagnosed nonskin malignancy among men in the United States. It had been estimated that 161,360 men would be diagnosed with this cancer during 2017, and 26,730 of already-involved patients would expire during the same year.[1] The incidence is relatively higher among the elderly, and as the life expectancy increases in populations, it is assumed that PC will be an even greater health issue, especially in developed countries.[2] Twenty percentage of the newly diagnosed patients already have evidence of regional invasion or distant metastasis.[1] In addition, 30–50% of patients who underwent localized cancer therapy later would manifest recurrence of systemic disease.[3,4] Unlike the early disease, in the metastatic setting, the mainstay of systemic treatment is the androgen deprivation therapy (ADT), and when encountered resistance, it is the conventional chemotherapy using taxane-based regimens.[5–8] A recent meta-analysis has shown longer overall survival (OS) and radiographic progression-free survival (PFS) in patients receiving ADT.[9] Another meta-analysis has also proven the superiority of ADT (whether luteinizing hormone release hormone agonists or antiandrogens) over orchiectomy and even combined androgen blockade.[10] ADT is very

* Corresponding author. Students' Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail addresses: mmz4566@gmail.com (M. Mohammadzadeh), as4007@yahoo.com (M. Shirmohammadi), ghojazadehm@hotmail.com (M. Ghojazadeh), nikniazleila@gmail.com (L. Nikniaz), mortaza_raeisi@yahoo.com (M. Raeisi), mousavi.ag@tbzmed.ac.ir (S.A.M. Aghdas).

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effective in about 75% of metastatic patients.[11] The latest data suggest that about 20% of patients undergoing the optimal treatment for PC will develop CRPC within 5 years. The median survival for mCRPC is estimated to be 15–36 months in recent studies.[12] Enzalutamide is an oral androgen receptor inhibitor used in mCRPC and has shown to be very beneficial in postponing chemotherapy and prolonging radiographic PFS.[13]

There is a need for more sophisticated methods in the systemic treatment of this particular mCRPC population. Currently, most of the targeted therapy strategies are aimed at the prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein with a dominantly heavier extracellular domain consisting of 707 amino acid residues.[14] PSMA is overexpressed in most types of the PCs. This was previously proven by pathology studies and nowadays by PSMA-targeted positron emission tomography imaging.[15–17] It contains a number of immunogenic HLA-A0201–restricted epitopes, which makes it a good candidate for immune-mediated anticancer agents.[18] Dendritic cells (DCs) are extremely efficient antigen presenting cells (APCs) and essential links between innate and adaptive immune system. Because the tumor cells do not sufficiently present antigens themselves, researchers have been trying to use DCs as vaccines against variety of cancers over the last decades. In fact, Sipuleucel-T, autologous APCs activated by PA2024, has already proven its clinical efficacy in the treatment of mCRPC.[19] By activating $CD8^+$ (cytotoxic) T-lymphocytes, DCs induce tumor-specific immunity.[20] The goal is to reduce cancer burden by building effector T-cells and ideally establishing antitumor immune memory to prevent future recurrences.[21] Although over 20 years has passed since the first trial using DCs in treatment of mCRPC was conducted, no meta-analysis study has ever analyzed the results from these studies, and the efficacy of this modality is with ambiguity. Therefore, we have gathered and analyzed data from clinical studies investigating the antitumor efficacy of DCs pulsed with PSMA in treatment of mCRPC patients.

2. Materials and methods

2.1. Literature search

Published clinical studies were collected by searching PubMed/Medline, Scopus, Embase, Cochrane Library, internation scientific indexing (ISI) Web of Science, ProQuest, and Google Scholar. We also searched for trials registered in clinical trial registries and abstracts presented in American Society of Clinical Oncology. In addition, the reference lists of all retrieved studies were checked to identify additional relevant studies for inclusion. In general, our search strategies in each database were combinations of the following keywords: “prostate cancer,” “prostate specific membrane antigen,” “targeted therapy,” “dendritic cell”. Database search had no limitation in time, and our last update on searches was in February 2017. Our search strategies are available in supplementary files.

2.2. Eligibility criteria

We included phase I and II clinical trials that had enrolled patients with mCRPC. CRPC is defined as “PC progression despite castrate levels of testosterone” by the Prostate Cancer Clinical Trials Working Group, and when metastases are present, the term mCRPC is used.[22] To the best of our knowledge, no randomized clinical trial has been conducted to investigate the role of DCs pulsed with PSMA in treatment of mCRPC. Our inclusion criteria were clinical trials in the English language that had studied the antitumor effects of DCs pulsed only with the extracellular portion of PSMA for treatment of mCRPC patients. We excluded trials that had used PSMA as an imaging target or in the treatment of malignancies other than PC. Studies using DCs pulsed with PSMA along with multiple other tumor antigens were excluded to avoid false response. In addition, all non-English studies were excluded. Because all of the studies included nonrandomized cohorts, we freely selected patients who received the investigational agent as our sample population.

2.3. Data collection and statistical analysis

Two review authors independently collected data about publication year, the country in which participants were recruited, and the baseline characteristics of patients including age, Karnofsky performance score (KPS) (if reported), prior treatments (radical prostatectomy, hormone ablation therapy, chemotherapy, and radiotherapy), baseline prostate-specific antigen levels (if reported), and metastasis sites. When the follow-up period was not clearly stated, we reported the longest follow-up presented in the articles. We performed an intention-to-treat analysis whenever possible. Two reviewers (SAMA and MR) independently extracted the data of interest, and when there was an inconsistency in data, MM rechecked the data, and agreement was reached in a team session. To analyze the data, we used Comprehensive Meta-Analysis software, version 2.0. A P value of <0.05 was considered to be significant. Heterogeneity was measured by the Cochran's Q test and I^2 test. I^2 index of <25% was indicative of negligible heterogeneity; the range of 25–75%, moderate heterogeneity; and >75%, significant heterogeneity. If there was a significant heterogeneity, random model method was applied to analyze the data. Egger's regression test and funnel plot were used to evaluate the publication bias.

2.4. Outcomes

The primary outcome was the antitumor response, obtained from blood prostate-specific antigen (PSA) level changes and evidence from imaging studies. We accepted patients with complete response, partial response, and stable disease (defined as stable PSA levels and no enlargement in lesions and no newly developed lesions) as our response population. We believe that stabilizing the progressive disease is of value in mCRPC patients and can prolong the OS and improve the quality of life. Our secondary outcome was to evaluate the drug toxicities of grade $\geq$3 and OS in sample populations.

3. Results

3.1. Trial flow and eligible studies

The Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram is presented in Fig. 1. The initial number of studies gathered from databases was 4,691. After deleting the duplicate articles, 3,684 remained. We screened the abstracts of these studies and selected clinical studies, in which the effect of PSMA-targeted therapies was investigated in PC patients. Of 37 studies meeting these criteria, only 10 had used DCs pulsed with PSMA. Two of these studies had used DCs pulsed with multiple antigens and were not included in the analysis.[23,24] One study had administered additional granulocyte-macrophage colony-stimulating factor (GM-CSF) and was excluded from the analysis.[25] Another study had provided very little data about the patients and lacked the sufficient quality to be included in the study.[26] We accepted six trials eligible for analysis overall reporting on 153 mCRPC patients treated with adequately similar numbers of DCs pulsed with PSMA peptides (PSM-P1 or PSM-P2). Characteristics of

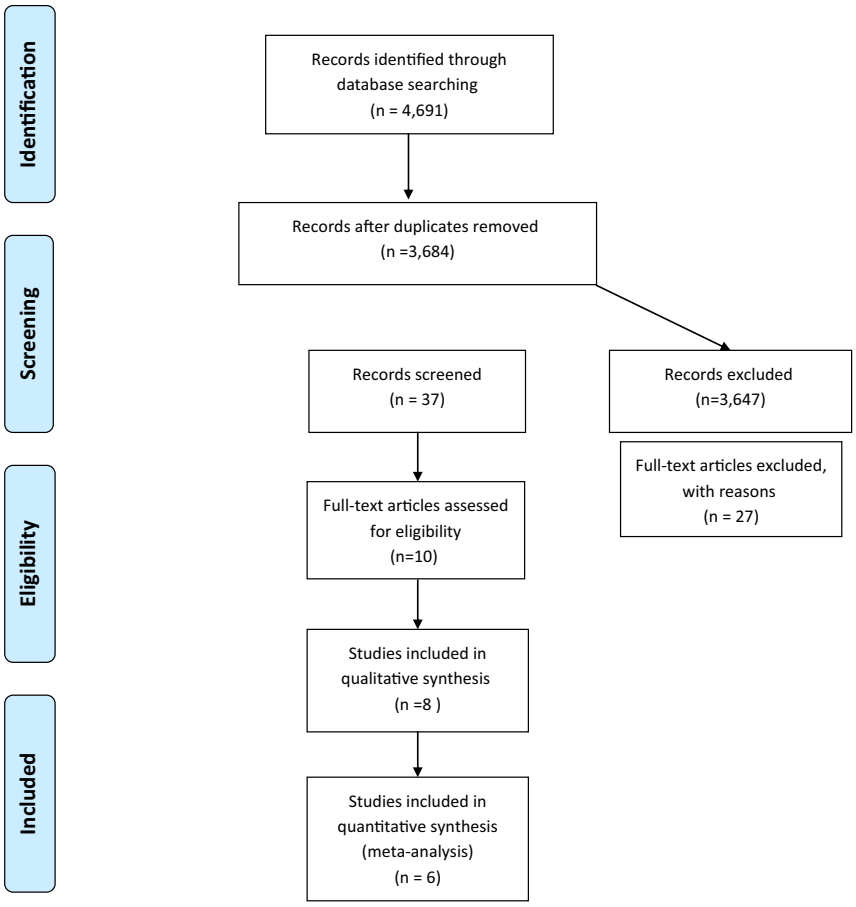

Fig. 1. Flow diagram for selection of articles. 4,691 articles werefound in total. We searched PubMed/Medline, Scopus, Embase, Cochrane Library,ISI Web of science, Proquest and Google scholar, ASCO and clinicaltrials.gov.After excluding duplicate articles, 3,684 articles remained for abstractscreening. At this level, we accepted any clinical study that investigated theeffect of PSMA-targeted therapies on prostate cancer patients for full-textscreening, including 37 articles. During studying the full-texts, only trialsthat had studied the efficacy of PSMA-pulsed DCs on mCRPC patients wereselected for eligibility assessment. Of 10 studies, 2 had studied the efficacyof DCs pulsed with multiple cancer specific antigens that were excluded fromthe study. Of remaining 8 studies, one had administered additional GM-CSF, andone had not provided any data about the patients and lacked the sufficientquality, which were excluded from quantitative analysis.

the six nonrandomized prospective cohort trials included for the review are summarized in the Table 1.[25,27–31] Of these six studies, except for two studies having five and two groups of intervention, all other studies were single armed. Because of the aggregate nature of data, we could not identify patients positive for HLA-A0201 although the inclusion criteria among studies were similar enough to avoid significant bias. Theoretically, patients positive for human leukocyte antigen (HLA)-A0201 may have a greater response rate than patients lacking this HLA.[32] In most trials, response to treatment was evaluated by criteria from National Prostate Cancer Project. The primary endpoint was disease progression after treatment with the investigational agent, determined by continuous PSA-level measurements or imaging studies (using bone scan or ProstaScint scan). These criteria almost meet the newer criteria defined by the Prostate Cancer Clinical Trials Working Group 3 on disease progression.[33] The study by Murphy et al (1996) had five treatment arms, in which only group 4 and 5 had been injected with DCs.[32] Thus, only those two groups were included in our analysis. The average number of cells infused in groups 4 and 5 was 8.2×10^6 and $7.3 \times l0^6$, respectively. In Murphy et al's (1999) study, the average number of infused DCs was 1.7×10^7.[27] In spite of the higher number of infused DCs (in contrast to their prior study), the response population was smaller. In all studies, DCs were obtained by leukapheresis, and each patient was infused with his own autologous cells. The general immune response was measured by delayed-type hypersensitivity skin test. It has been shown that the majority of the responder population has positive results in this test.[27] In addition, the response population kept this positive result for longer periods, and this was sometimes related to lower PSA levels in this population for longer periods. No significant adverse effects have been reported in the included studies. Only two studies reported the OS of the sample population; Hemstreet et al reported OS of 25.1 months, and Tjoa et al (1999) reported OS of 4.8 months (which are not presented here).[25,31] However, these reports are significantly heterogenous in nature and most probably not reliable. The study by Tjoa et al (1999) had used GM-CSF in combination with DCs and was not included in the analysis. One of the included studies concluded that administering GM-CSF in addition to DCs does not improve the clinical outcomes.[28] Duration of response varied extensively among patients, from less than 100 days to more than 300 days.[30] Data from one study that had five treatment arms showed that arm 4 and 5 in which patients received DCs pulsed with PSM-P1 and 2 had larger rate of response in contrast to arms 1, 2, and 3 in which patients received only PSM-P1 and 2 without pulsation of DCs.[29] Some of the included studies had noted that bone pains in patients had declined following treatment with DCs. Unfortunately, there were no data about the sites of metastasis, and only one study had mentioned the baseline levels of PSA. Because criteria used for assessing patients' performance were different among studies

Table 1
Summary of patient data and results of studies assessing dendritic cell therapy antitumor effect in mCRPC patients.

Author/Year	Country	Duration of follow up (days)	Control Group/Intervention Group											Overall survival median (months)	Response*	Toxicity grade ≥3
			Patients	Age median	KPS median	Primary prostatectomy	Prior HT_x	Prior CT_x	Prior RT_x	Bone Metastasis	Soft tissue Metastasis	PSA_1 Median (ng/ml)	Intervention or Investigational Agent			
Hemstreet et al (2013)	USA [31]	N/A	8	68.5		2 (25%)	5 (62.5%)	5 (62.5%)	6 (75%)			9.75	Hyper Acute-Prostate immunotherapy	25.1	3 (37.5%)	Lymphopenia in 1 patient
Murphy. et al (1996)	USA [32]	225	19			7 (36.8%)			15 (78.9%)				DC pulsed with PSM-P1 and -P2		8 (42.1%)	None
Murphy. et al (1999)	USA [27]	335	25	63		7 (28%)	13 (42%)		5 (20%)				DC pulsed with PSM-P1 and -P2		9 (36%)	N/A
Simmons. et al (1999)	USA [28]	N/A	51										DC pulsed with PSM-P		37.2%	None
			44										DC pulsed with PSM-P+ GM-CSF		20.5%	Mild fever, fatigue, pain, local reactions
Tjoa et al (1997)	USA [29]	370	19			7 (36.84%)	19 (100%)		15 (78.9%)				DC pulsed with PSM-P1 or -P2		8 (42.1%)	N/A
Tjoa. et al (1998)	USA [30]	250	33	72									DC pulsed with PSM-P1 or –P2		20 (60.6%)	N/A

* We accepted stable disease, partial response and complete response as response group. The criteria for determining response was from NCPC. KPS: Karnofsky performance score, HT: Hormone therapy, CT: Chemotherapy, RT: Radiotherapy, PSA_1: serum level of Prostate Specific Antigen prior to investigational treatment, GM-CSF: granulocyte-macrophage colony-stimulating factor.

including KPS and Eastern Cooperative Oncology Group, we could not report the exact scores of sample populations' performance. However, we do assume that all patients had at least 70% of KPS. Owing to lack of sufficient data, we could not achieve our secondary goals.

3.2. Meta-analysis of the primary outcome

No significant between-study heterogeneity or inconsistency was detected by Cochran's Q test or I^2 test ($I^2 = 5.47\%$; $Q = 5$; $P = 0.382$), indicating that the trials were similar enough to be combined (Table 2). The event rate of 0.43 (95% confidence interval, 0.355–0.512) represents the fraction of sample mCRPC patients responding to the targeted therapy by DCs pulsed with PSM-P1 or -p2. The pooled results were not statistically significant because of the *P*-value of 0.097. The forest plot is shown in Fig. 2.

3.3. Publication bias

We used Egger's test to check for probable publication bias in our study. In addition, the funnel plot is presented in Fig. 3. Two studies (Tjoa 1997 and Murphy 1996) had equal event rates and *P*-values. Thus, they are overlapped and shown as one point in the plot. Because the number of trials included in this study is less than the recommended minimum number of 10 trials, statistical tests for publication bias can be potentially unreliable.[34]

4. Discussion

MCRPC is not considered curable, and the treatment goal is generally prolonging the survival as long as possible and increasing the quality of lives of patients. As mentioned previously, there is need for more effective treatments, more capable of shrinking visceral and bone lesions, prolonging PFS, and having less adverse effects, in contrast to the conventional chemotherapies. We performed a systematic review and meta-analysis of the published literature presented in major databases, registered trials, and abstracts presented at the American Society of Clinical Oncology meetings to identify all the trials related to our subject. By combining the data from the selected trials, we demonstrated that 43% of the mCRPC patients have shown a response to the treatment by gaining at least a stable disease. In contrast, previous trials have reported that about 50% of mCRPC patients who received docetaxel experienced >50% reduction in PSA levels.[6,35] Some of the studies had noted improvements in the quality of life by reduction in bone pains after treatment with DCs. However, the *P*-value for our results was not significant. No significant adverse effects were reported regarding this treatment in any of the included studies although a study on the role of DCs in the therapy of cancer has reported fever, insomnia, anorexia joint soreness, and skin rashes as the major side effects of this modality.[36]

A pathology study has revealed the heterogenous and even negative staining of PSMA in more than 10% of the primary tumor and distant metastasis samples, which can explain a proportion of treatment failures of targeted therapies.[37] Patients negative for HLA-A*0201 had higher rates of treatment failure, and probably in future, the use of these DCs will be limited to patients positive for this HLA. Other pathology studies have estimated positive staining of approximately 95% of all PC tissues for PSMA and its correlation in intensity with higher Gleason score and shorter relapse time after prostatectomy.[38–40] Although it has been shown that PSMA is also expressed in the small intestine, proximal convoluted tubules of the kidneys, salivary glands and brain, the level of expression in these tissues are 100- to 1,000-fold less than that in the prostate tissue.[41] Thus, any targeted therapy directed to this antigen would

Table 2
Statistical tests for heterogeneity.

Number of studies	Effect size and 95% interval			Test of null (2 tailed)		Heterogeneity			
	Point estimate	Lower limit	Upper limit	Z-value	*P*	Q-value	df (Q)	*P*	I^2
6	0.432	0.355	0.512	−1.66	0.097	5.29	5	0.382	5.47

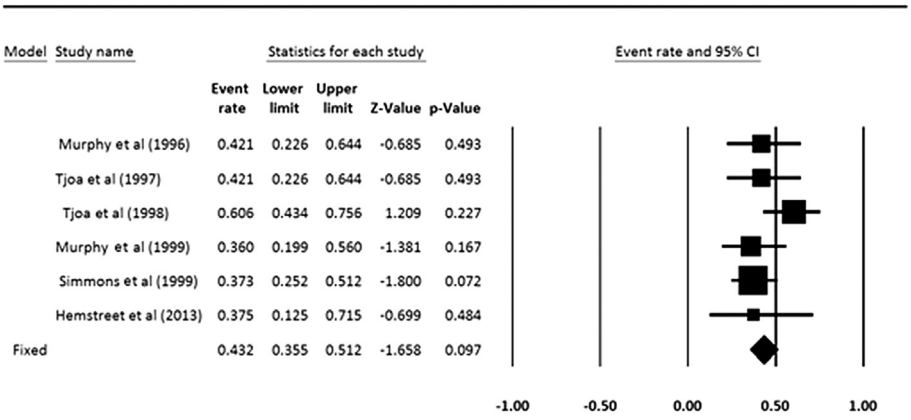

Fig. 2. Results from meta-analysis of event ratefor antitumor response in patients.

leave minimal adverse effects on these organs. Especially, because the majority of these patients are elderly and their tolerance to toxic side effects is low, light side-effect profile of new therapeutics is of great significance. MXXXL motif in the cytoplasmic tail of the antigen mediates the internalization by clathrin-coated pits, suggesting that PSMA can be used as a mediator for intracellular delivery of cytotoxic and radioactive agents.[42–45] We believe that radioimmunotherapies using J591 antibody may be more beneficial for mCRPC patients. Clinical trials are ongoing, and promising results have been published. Theoretically, even if some populations of tumor cells fail to express the PSMA, the radioactivity from the nearby cells that express PSMA will eradicate these cells, and this modality may be able to overcome the heterogeneity in high-grade metastatic lesions. Many types of carcinomas also express PSMA in their neovasculature, suggesting the possible efficacy of targeted therapies against this antigen in those cancers.[46–50]

A study of our inclusion had reported the OS of 25.1 months for patients receiving the investigational treatment, a much longer period in contrast to results from a meta-analysis study presenting OS of 18.4 and 15.1 months for patients receiving enzalutamide and cabazitaxel, respectively. However, the results from these studies cannot be compared because of very small sample size and weaker study design in the first study in contrast to the second.[9,31] There is a necessity to compare the survival benefits and antitumor efficacy of these DCs with the conventional chemotherapy regimen. Although a recent cohort study has shown 11 months longer median OS for patients receiving DCs pulsed with recombinant PSMA (rPSMA) and recombinant survivin (rSurvivin) peptides in contrast to the control group receiving docetaxel plus prednisone, the sample size of 11 patients per arm is too small to accept the results of this study as a generalizable answer.[51] Two excluded studies had used DCs simultaneously pulsed with prostate stem cell antigen, prostatic acid phosphatase, PSMA, PSA, transient receptor potential p8 (trp-p8), prostein, and rSurvivin.[23,24] Obviously, their results were not representative of the absolute anti-PSMA immunization. However, this method seems to be more effective, and future studies should try to investigate this synergic effect on prolonging the OS and PFS. A future research topic can be the evaluation of the role of DCs pulsed with multiple cancer-specific antigens in preventing disease recurrence in prostatectomized nonmetastatic patients.

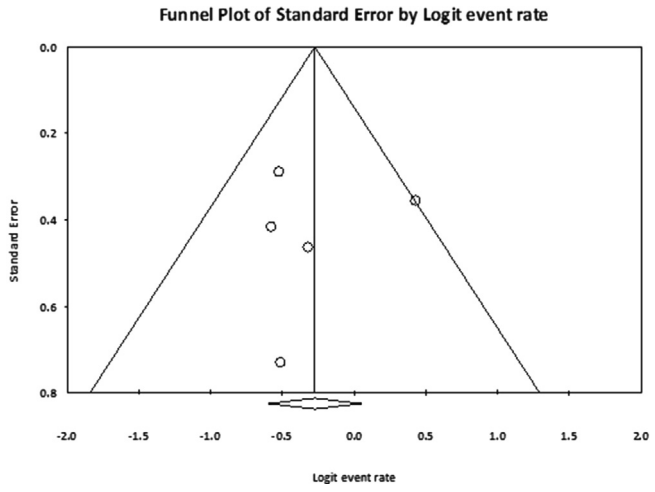

Fig. 3. Funnel plot of the 6 studies, disprovingany significant publication bias. Note that two studies had equal event ratesand p-values. Thus, they are completely overlapped in the plot.

In general, there was little evidence of heterogeneity or publication bias that may have affected our results. The lack of heterogeneity was further supported by the equality of results from random- and fixed-effect models. The limitations of our study are the relatively low number of sample size pooled from the trials, single-arm structure of the studies, inadequate data about the baseline status of patients (including baseline PSA level and related Gleason scores), absence of individual-level patient data including the proportion of patients positive for HLA-A*0201, numbers of DCs each participant was infused with, previous treatments, and exclusion of non-English studies.

5. Conclusions

Although our study was inconclusive due to the insignificant *P*-value, it revealed that in 43% of mCRPC patients, administration of

the aforementioned DCs may lead to at least stable disease. As a major advantage over chemotherapy, this treatment modality causes minimal adverse effects. Some studies have revealed that pulsing DCs with multiple tumor antigens can be more effective in contrast to single-antigen pulsation. We strongly believe that the future of care for cancers especially in the setting of metastatic disease lies in the individualized targeted therapies aimed at tumor-specific antigens determined by Immunohistochemistry (IHC) of the individual's tumor.

Conflicts of interest

None of the authors had a conflict of interest with respect to this manuscript.

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