REVIEW ARTICLE

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Immunotherapy with Sipuleucel-T (APC8015) in patients with metastatic castration-refractory prostate cancer (mCRPC): a systematic review and meta-analysis

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ABSTRACT

Objective: To perform a systematic review and meta-analysis of all randomized controlled trials comparing the efficacy of Sipuleucel-T versus placebo for asymptomatic or minimally symptomatic metastatic castration-refractory prostate cancer (mCRPC).
Materials ans Methods: Several databases were searched, including MEDLINE, EMBASE, LILACS, and CENTRAL. The endpoints were overall survival (OS), time to progression (TTP) and side effects. We performed a meta-analysis (MA) of the published data. The results are expressed as Hazard Ratio (HR) or Risk Ratio (RR), with their corresponding 95% confidence intervals (CI 95%).
Results: The final analysis included 3 trials comprising 737 patients. The TTP was similar in patients who received Sipuleucel-T or placebo (fixed effect: HR = 0.89; CI 95% = 0.75 to 1.05; p = 0.16), with no heterogeneity detected on this analysis (Chi2 = 2.14, df = 2 (P = 0.34); I2 = 6%). The results showed a higher overall survival in patients treated with Sipuleucel-T (fixed effect: HR = 0.74; CI 95% = 0.61 to 0.89; p = 0.001; NNT = 3). We found no heterogeneity on this analysis either (Chi2 = 1.46, df = 2 (P = 0.48); I2 = 0%). The incidence of adverse events (grade > 3) was the same in both groups.
Conclusion: Sipuleucel-T prolongs overall survival in patients with asymptomatic or minimally symptomatic mCRPC.

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INTRODUCTION

Prostate cancer is the most common non-cutaneous malignancy and the second leading cause of cancer mortality amongst men in the Western world (1). Up to 40% of men diagnosed with prostate cancer will eventually develop metastatic disease (1). Although androgen deprivation is the standard of care for advanced prostate cancer, patients with metastatic disease eventually progress to a castration-resistant state (2,3).

The average survival for patients with metastatic castration-refractory prostate cancer (mCRPC) is 2 to 3 years (1). Other denominations have also been used in the definition of CRPC, including: hormone-resistant prostate cancer, hormone-refractory prostate cancer, hormone-independent prostate cancer and androgen-independent prostate cancer. CPRC is the most widely accepted term, because even those patients considered resistant to castration, may still show some response to secondary hormonal manipu-

lations as documented in studies with new drugs such as Abiraterone (4) or MDV3100 (5).

Until recently, we have had few effective therapeutic options for the management of CRPC. Mitoxantrone was the first chemotherapeutic agent that demonstrated clinical activity in CRPC; it was approved in 1996 based on a reportedly improved quality of life (6). New treatment strategies have since been developed. Docetaxel was shown to modestly improve overall survival (OS) in two phase III trials (7,8). Based on these results, docetaxel chemotherapy was approved in 2004 by the US Food and Drug Administration (FDA) as the first-line standard treatment of mCRPC (9).

In 2010, the autologous cellular immunotherapeutic product Sipuleucel-T also received FDA approval for use in patients with asymptomatic or minimally symptomatic mCRPC. This approval indicates immunotherapy as a feasible treatment for CRPC patients (10,11). Currently, most studies are investigating the real efficacy of immunotherapy in patients with metastatic CRPC (11).

Sipuleucel-T, also referred to as APC8015, is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen-presenting cells, that have been activated in vitro with a recombinant fusion protein. The recombinant fusion protein PA2024 is composed of prostatic acid phosphatase, an antigen expressed in the majority of prostate adenocarcinomas (12-14).

The first randomized study, published in 2006, showed an increase of 4.5 months in median overall survival, in favor of Sipuleucel-T in patients with mCRPC (15).

However, 3 years later, the final results of the study D9902A were presented and no differences were observed in overall survival between the groups evaluated (14).

In 2010, a larger phase III study, the IMPACT trial, was subsequently published and showed an increase of 4.1 months in median overall survival in favor of the Sipuleucel-T group (16).

To confirm these survival findings, our objective was to analyze all published randomized controlled trials (RCTs) that compared the efficacy of Sipuleucel-T against placebo for asymptomatic or minimally symptomatic mCRPC.

MATERIALD AND METHODS

Study Selection Criteria

Types of Studies

We included RCTs with parallel design that compared the use of Sipuleucel-T (autologous active cellular immunotherapy) and placebo.

Types of participants

The selected studies included patients with radiologic evidence of metastases, asymptomatic or minimally symptomatic castration-refractory prostate cancer (progressive disease with serum testosterone level of less than 50 ng/dL or 17 nmoL/ liter) and without visceral metastases.

Search strategy for identification of studies

A wide search on the main computerized databases was conducted, including EMBASE, LILACS, MEDLINE, SCI, CENTRAL, The National Cancer Institute Clinical Trials service, and The Clinical Trials Register of Trials Central. In addition, the abstracts published in the proceedings of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), Society of Urologic Oncology (SUO) were also searched.

For MEDLINE, we used the search strategy methodology for randomized controlled trials (17) recommended by the Cochrane Collaboration (18). For EMBASE, we used adaptations of this same strategy (17), and for LILACS, we used the search strategy methodology reported by Castro et al. (19). We performed an additional search on the SCI database looking for studies that were cited on the included studies. We added the specific terms pertinent to this review to the overall search strategy methodology for each database.

The overall search strategy was as follows: #1 ("Immunotherapy"(Mesh) AND "Prostatic Neoplasms"(Mesh); #2 Random*

Searches of electronic databases combined the terms: #1 AND #2 for these study designs:

Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, and Review.

Critical Evaluation of the Selected Studies

All the references retrieved by the search strategies had their title and abstract evaluated by two of the researchers. Every reference with the least indication of fulfilling the inclusion criteria was listed as pre-selected. We retrieved the complete article of all pre-selected references. They were analyzed by two different researchers and included or excluded according to the previously reported criteria. The excluded trials and the reason of their exclusion are listed in this article. Data was extracted from all the included trials.

Details regarding the main methodology characteristics empirically linked to bias (20) were extracted with the methodological validity of each selected trial assessed by two reviewers (T.E.A.B and O.C). Particular attention was given to some items such as: the generation and concealment of the sequence of randomization, blinding, application of intention-to-treat analysis, sample size predefinition, loss of follow-up description, adverse events reports, if the trial was multi-centric and the sponsorship.

Data Extraction

Two independent reviewers extracted data. The name of the first author and year of publication were used to identify the study. All data were extracted directly from the text or calculated from available information when necessary. The data of all trials were based on the intention-to-treat principle, so they compared all patients allocated in one treatment with all those allocated in the other.

The primary endpoints were overall survival (OS) and time to progression (TTP). TTP was defined as the time from randomization to the time of disease progression. Disease progression included any of the following: 1) progressive disease on serial radiographic imaging tests; 2) new cancer-related pain associated with a radiographic anatomical correlation; or 3) other clinical events consistent with progression such as spinal cord compression, nerve root compression, or pathologic fracture.

Other clinical outcomes evaluated included the number of patients that presented adverse events (AEs) (grade ≥ 3): chills, fatigue, fever (pyrexia), back pain, headache, arthralgia, asthenia, nausea, anemia, vomiting and prostate-specific antigen (PSA) reduction of ≥ 50%.

Analysis and Presentation of Results

Data were analyzed using the Review Manager 5.0.24 statistical package (Cochrane Collaboration Software) (21).

Dichotomous clinical outcomes are reported as Risk Ratio (RR) and survival data as Hazard Ratio (HR) (22). The corresponding 95% confidence interval (CI 95%) was calculated, considering P values less than 5% ($p < 0.05$). A statistic for measuring heterogeneity was calculated through I2 method (25% was considered low-level heterogeneity, 25-50% moderate-level heterogeneity and > 50% high-level heterogeneity) (23,24).

To estimate the absolute gains in TTP and OS, we calculated the meta-analytic survival curves as suggested by Parmar et al. (22). A pooled estimate of the HR was computed by a fixed-effect model according to the inverse-variance method (25). Thus, for effectiveness an HR or RR greater than one favors the standard arm (Placebo) whereas an HR or RR less than 1 favors the Sipuleucel-T treatment.

If statistical heterogeneity was found in the meta-analysis, we performed an additional analysis using the random-effects model described by DerSimonian and Laird (26), that provides a more conservative analysis.

To assess the possibility of publication bias, we performed the funnel plot test described by Egger et al. (27). When the pooled results were significant, the number of patients needed to treat (NNT) to cause or to prevent one event was calculated by pooling absolute risk differences in trials included in meta-analyses (28-30). For all analyses, a forest plot was generated to display results.

RESULTS

The diagram represents the flow of identification and inclusion of trials, as recommended by the PRISMA statement (Preferred Reporting

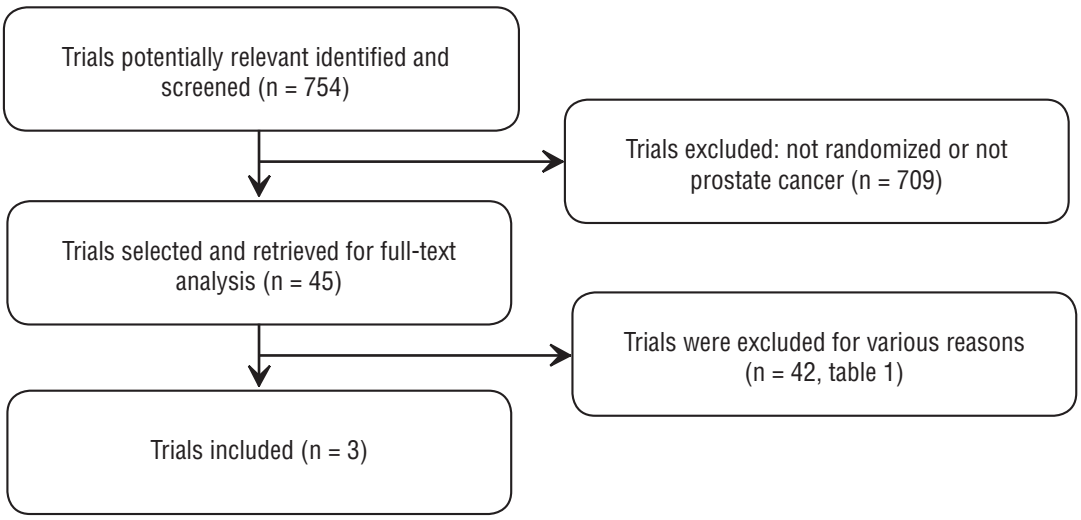
Items for Systematic Reviews and Meta-Analyses) (31) (Figure-1).

Overall, 754 references were identified and screened.

Forty-five studies were selected and retrieved for full-text analysis. Of these studies, 42 were excluded for various reasons, described on Table-1 (additional material).

The final analysis included 3 trials comprising 737 patients. All trials were randomized (Sipuleucel-T or control), double-blinded, placebo-controlled and multi-centric. The primary endpoint was TTP in two studies (14,15) and OS in one study (16) (Table-2).

Figure 1 - Trial selection flow.



Patients were randomly assigned in a 2:1 ratio to receive either Sipuleucel-T or placebo every 2 weeks, for a total of three infusions. In all studies, concurrent bisphosphonates therapy and previous chemotherapy were allowed, but patients with visceral metastases were excluded (14-16).

Patients without prior bilateral orchiectomy continued on gonadal suppression with a luteinizing hormone-releasing hormone agonist throughout the trials. In all studies, pretreatment was performed with acetaminophen and an antihistamine such as diphenhydramine (14-16).

Reductions in PSA levels ≥ 50% were equally detected in both groups (fixed effect: RR = 0.98; CI 95% = 0.96 to 1.00; p = 0.07). We found no heterogeneity on this analysis (Chi^2 = 0.68, df = 1 (P = 0.41); I^2 = 0%) (Figure-2).

The TTP was similar in patients who received Sipuleucel-T or placebo (fixed effect: HR = 0.89; CI 95% = 0.75 to 1.05; p = 0.16) without indications of heterogeneity on this analysis (Chi^2 = 2.14, df = 2 (P = 0.34); I^2 = 6%) (Figure-3).

The results showed a higher overall survival in patients treated with Sipuleucel-T (fixed effect: HR = 0.74; CI 95% = 0.61 to 0.89; p = 0.001; NNT = 3), again without heterogeneity (Chi^2 = 1.46, df = 2 (P = 0.48); I^2 = 0%) (Figure-4).

The incidence of grade ≥ 3 adverse events was the same in both groups: chills (RR = 6.13; CI 95% = 0.81 to 46.73), fatigue (RR = 0.94; CI 95% = 0.26 to 3.39), fever (pyrexia) (RR = 0.66; CI 95% = 0.16 to 2.61), back pain (RR = 0.89; CI95% = 0.40 to 1.98), headache (RR = 2.04; CI 95% = 0.23 to 18.12), arthralgia (RR = 0.96; CI 95% = 0.35

Table 1 - Characteristics of Excluded Studies.

Study	Reason for Exclusion
Beer 2011 (39)	Androgen-dependent prostate cancer
Sanda 1999 (40)	Not a randomized trial
Madan 2009 (41)	Not a randomized trial
Antonarakis 2010 (42)	Not a randomized trial
Cha 2011 (43)	Not a randomized trial
Joniau 2011 (44)	Not a randomized trial
Madan 2010 (45)	Not a randomized trial
May 2011 (46)	Not a randomized trial
Morse 2010 (47)	Not a randomized trial
McLeod 2011 (48)	A subgroup analysis
Fizazi 2011 (49)	Androgen-dependent prostate cancer
Beer 2011 (50)	Androgen-dependent prostate cancer
Penson 2006 (51)	Integrated analysis of studies analyzed (Small and Higano)
Sonpavde 2011 (52)	Not a randomized trial
Beltran 2011 (1)	Not a randomized trial
Drake 2010 (53)	Not a randomized trial
Cha 2010 (2)	Not a randomized trial
Harzstark 2009 (54)	Not a randomized trial
Mohebtash 2008 (55)	Not a randomized trial
Vaishampayan 2008 (56)	Not a randomized trial
Harzstark 2008 (57)	Not a randomized trial
Barqawi 2007 (58)	Not immunotherapy
Arlen 2007 (59)	Not a randomized trial
Di Lorenzo 2007 (60)	Not a randomized trial

Table 2 - Characteristics of Included Studies.

Study	N	Patients	Desing	Interventions	Primary endpoint
Small 2006 (15)	127	Asymptomatic metastatic CRPC	Randomized, double-blind, placebo-controlled, multicenter	Sipuleucel-T Placebo	Time to disease progression
Higano 2009 (14)	98	Asymptomatic metastatic CRPC	Randomized, double-blind, placebo-controlled, multicenter	Sipuleucel-T Placebo	Time to disease progression
Kantoff 2010 (16)	512	Asymptomatic or minimally sympto-matic CRPC	Randomized, double-blind, placebo-controlled, multicenter	Sipuleucel-T Placebo	Overall survival

Figure 2 - Comparative effect in reduction of PSA > 50% of Sipuleucel-T versus Placebo.

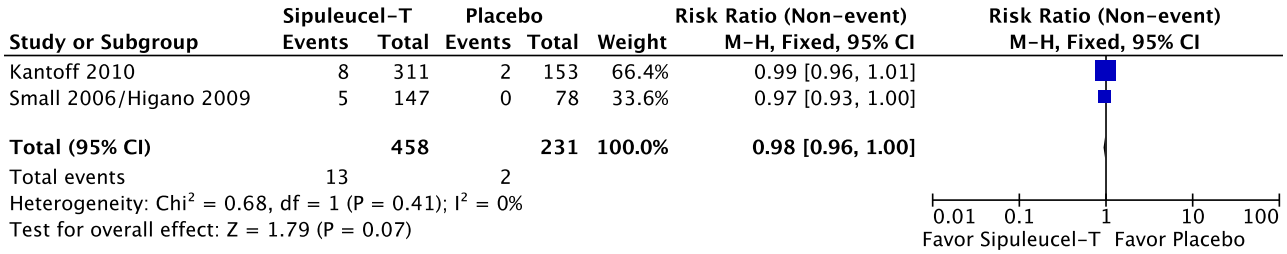


Figure 3 - Comparative effect in time to progression of Sipuleucel-T versus Placebo.

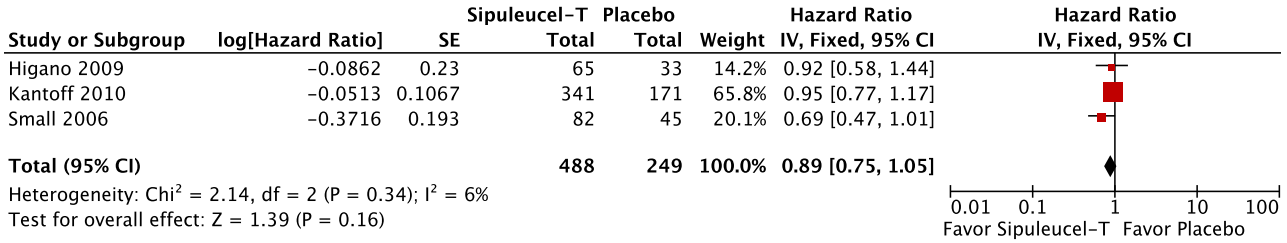
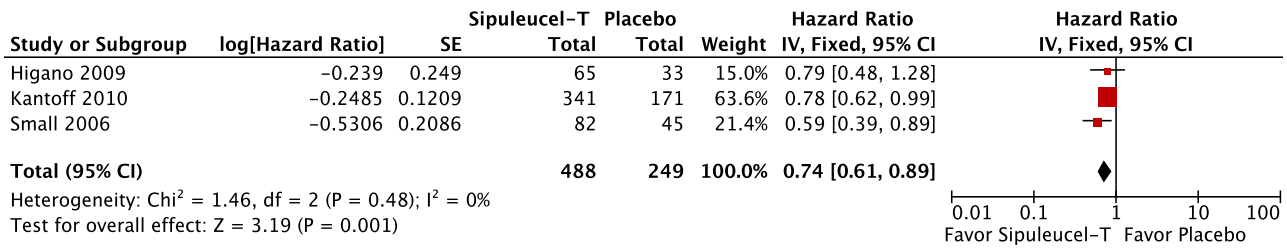


Figure 4 - Comparative effect in overall survival of Sipuleucel-T versus Placebo.



to 2.66), asthenia (RR = 1.49; CI 95% = 0.30 to 7.31), nausea (RR = 2.03; CI 95% = 0.23 to 18.10), anemia (RR = 0.78; CI 95% = 0.31 to 1.92) and vomiting (RR = 1.56; CI 95% = 0.06 to 37.86) (Figure-5).

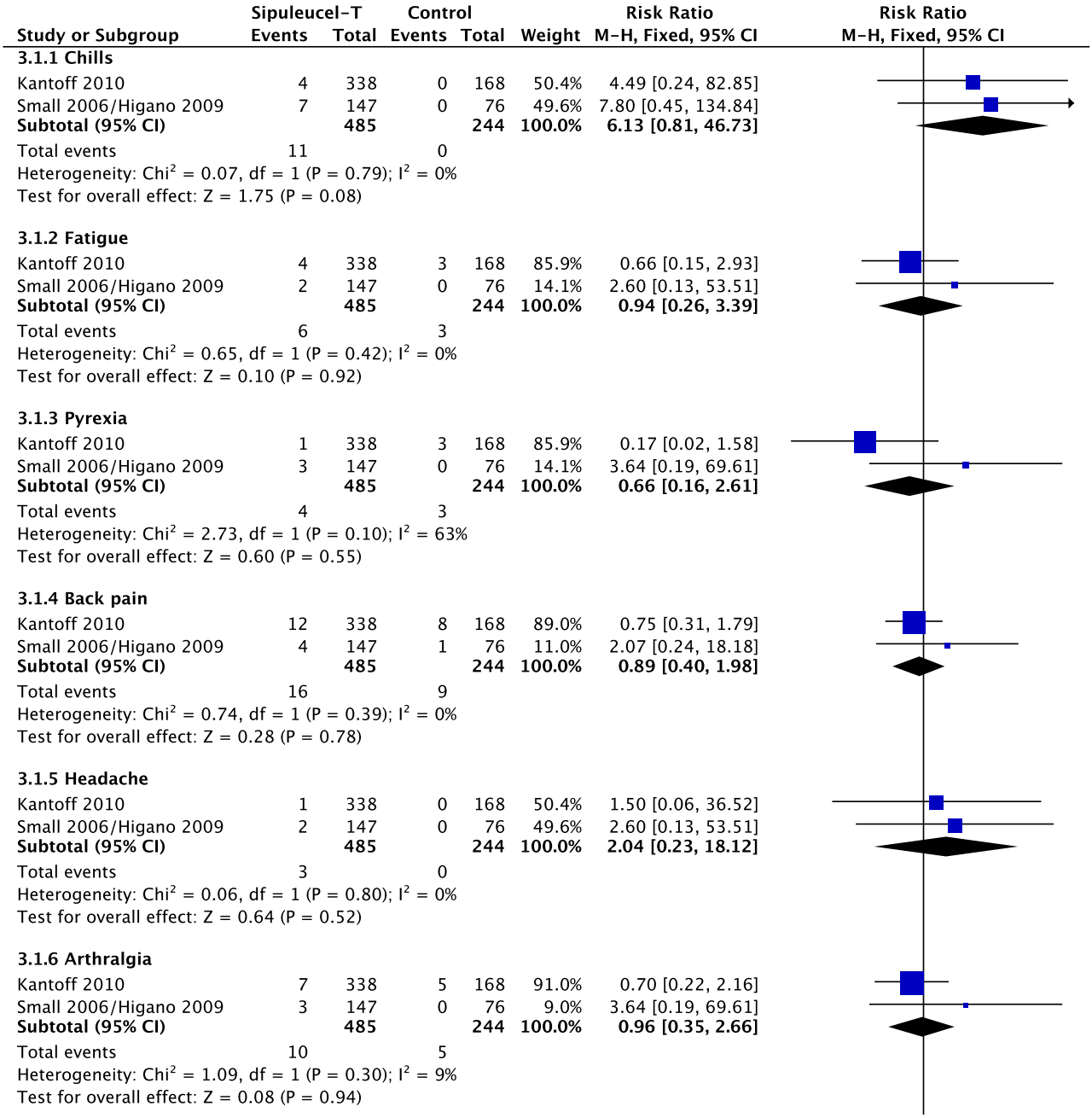
According to the funnel plot analysis (27) the possibility of publication bias was low for all of the endpoints.

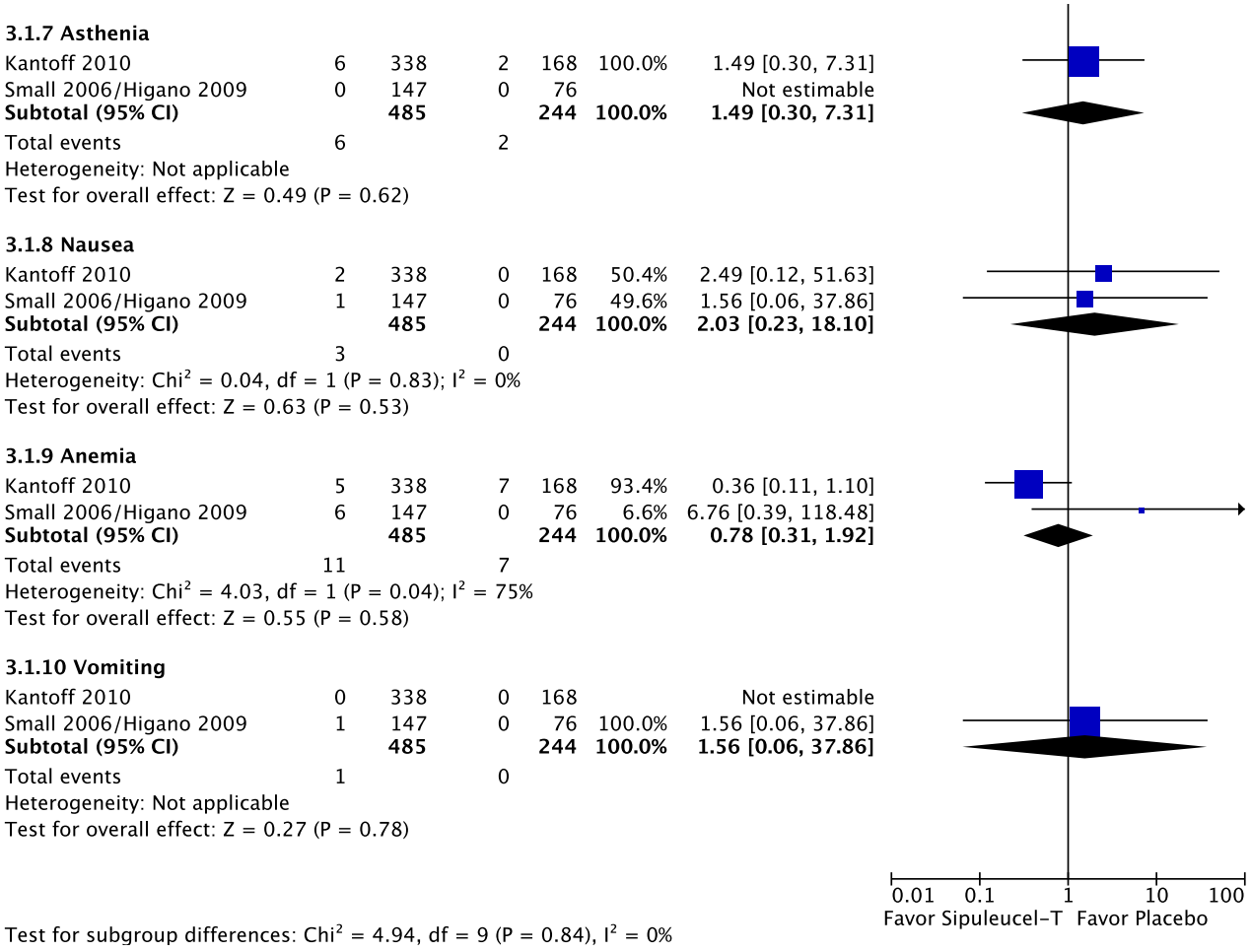
DISCUSSION

Vaccine-based therapies seek to directly stimulate a specific immune reaction against a single or multi-tumor antigens (11).

The four main types of vaccines that have been investigated for CRPC can be classified as

Figure 5 - Adverse events (grade > 3) of patients treated with Sipuleucel-T versus Placebo.





viral vector based, cell based, DNA vaccines, and autologous (derived from a patient's own tumor cells) (11).

Sipuleucel-T in this meta-analysis reduced the risk of death by 26%. In contrast to overall survival, the time to progression for the respective diseases and reduction in PSA levels did not differ significantly between Sipuleucel-T and placebo. This may be due to the delayed onset of antitumor responses after active immunotherapy, relative to objective disease progression (16). Other randomized clinical trials have also demonstrated that benefits in overall survival were not linked to effects in time to progression (32) or vice versa (16,33).

Similarly, PSA level declines have not consistently been a surrogate endpoint for survival, particularly in CRPC trials. The TAX327 trial is one example (34). In that trial, the docetaxel given every 3 weeks arm and the weekly docetaxel arm had essentially similar PSA > 50% decline rates (45% and 48%, respectively) yet only the every 3 week regimen demonstrated a survival advantage compared to mitoxantrone (35).

In the study by Kantoff (16) most patients had a PSA response rate measured at least twice during treatment. In the integrated analysis of two other studies included in this analysis (14) only 26% of patients had ≥ two PSA values measured at least 4 weeks apart. Therefore the PSA response rate may be underestimated (14).

The most common AEs associated with Sipuleucel-T treatment were chills, fatigue, fever (pyrexia), back pain, and headache. These AEs are generally consistent with cytokine release, as observed after the administration of other immunotherapies (36). Most AEs developed within one day

of infusion were grade 1/2 in severity and resolved in 2 days or less (37).

Docetaxel and Cabazitaxel, other FDA approved therapies that confer a survival advantage in mCRPC cases, are associated with grade 3/4 hematological toxicities and infections in 5% to 82% of patients (7,37,38). Abiraterone acetate, a potent inhibitor of CYP17 and androgen synthesis, also demonstrated improved survival in men with metastatic CRPC with progression after docetaxel chemotherapy. The most common adverse events included fluid retention, hypokalemia and hypertension (4). None of these have been compared in head to head trials or against Sipuleucel-T so we still do not know which is the better option.

Despite the encouraging results, there are many unresolved questions regarding immunotherapy, including the best clinical setting for immunotherapy (the rational combination and proper sequencing of Sipuleucel-T with other newly approved agents) and the definition of relevant clinical and immunological endpoints (2).

CONCLUSIONS

Sipuleucel-T prolongs the survival of patients with asymptomatic or minimally symptomatic mCRPC. The time to progression was the same of both groups. No grade 3/4 AEs were reported in 5% or more of patients.

CONFLICT OF INTEREST

None declared.

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