

Dexamethasone plus Somatostatin-analog Manipulation as Bone Metastasis Microenvironment-targeting Therapy for the Treatment of Castration-resistant Prostate Cancer: A Meta-analysis of Uncontrolled Studies

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Abstract. *Background:* Antisurvival factor therapy for prostate cancer cells (ASF) in castration-resistant prostate cancer, is a hormonal manipulation consisting of a somatostatin analog, which reduces the growth hormone-dependent, systemic IGF-1 production and of oral dexamethasone, which suppresses the urokinase type plasminogen activator-mediated "local" increase of IGF-1 bioavailability in the bone metastases, while the patients continue on a luteinizing hormone-releasing hormone analog therapy. *Aim:* To revisit relevant evidence and provide a quantitative summary estimate of ASF efficacy. *Materials and Methods:* A structured review of relevant literature and a meta-analysis of uncontrolled studies and cohorts within trials was carried out at tertiary academic centers. A computerized literature search was conducted in the electronic database Medline from inception to January 2012. To be eligible for inclusion, a study had to report data on the efficacy of ASF in the treatment of castration-resistant prostate cancer, independently of study design or duration. Data synthesis was performed using restricted maximum-likelihood random effects model. *Results:* Four studies fulfilled the inclusion criteria and were used for the evidence synthesis. The probability of a partial response within six months (defined as at least a 50% decrease

from baseline prostate-specific antigen concentrations) was 59.5% (95% confidence interval, 49.3% to 69.3%). No evidence of heterogeneity was noted (I^2 0%). The response noted did not persist over time (median progression-free survival of seven months and median overall survival of 16 months). The uncontrolled nature of the evidence and the paucity of other outcomes of interest need to be taken into account in the interpretation of the results. *Conclusion:* ASF manipulation is a safe alternative to standard therapy and induces partial remission lasting for at least six months. This partial response is consistently accompanied with an improvement in bone pain, performance status and quality of life.

Prostate cancer is a biologically heterogeneous disease associated with variable clinical outcomes. In patients with an aggressive disease, tumors initially confined to the prostate can spread to loco-regional lymph nodes and become disseminated to distant organs with a striking predilection for the skeleton (1-3). Skeletal metastases almost always represent the exclusive site of disease progression to castration-resistance (stage D3), whereby cancer cells escape from androgen withdrawal-induced apoptosis (4-6). Most prostate cancer-related deaths occur in patients with castration-resistant prostate cancer (5). Advances in the understanding of both the tumor's biological behavior and the skeletal micro-environment, with respect to the interaction between cancer cells and host tissue (7, 8), have facilitated the development of novel therapies for the treatment of castration-resistant prostate cancer (9, 10).

Efforts to confront the concerted interplay of tumor with the bone microenvironment, which avails the metastatic prostatic cells with a survival benefit, is not new. There is evidence suggesting that osteoblast-derived survival factors, such as insulin-like growth factor-1 (IGF-1), can protect human prostate cancer cells from chemotherapy-induced apoptosis

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(11). In addition, glucocorticoids down-regulate the expression of osteoblast-derived survival factors, as well as the prostate cancer cell-derived urokinase-type plasminogen activator, a regulator of both IGF-1 and the transforming growth factor-1 (TGF-1) bioavailability at the tissue level (12-14). Therefore, a combination therapy has been developed in an attempt to suppress the local bioavailability of IGF-1. This hormonal manipulation, also called antisurvival factor therapy (ASF), consists of a somatostatin analog (SM-A), which reduces the growth hormone (GH)-dependent systemic IGF-1 production, and of oral dexamethasone, which suppresses the urokinase-type plasminogen activator (uPA)-mediated local increase of IGF-1 bioavailability in the bone metastases (GH independent) (15), while patients with castration-resistant disease continue on a luteinizing hormone-releasing hormone analog (LHRH-a) therapy. The exploration of the potential efficacy of ASF, provided encouraging preliminary results (15, 16). Since relevant evidence is scarce, and since mostly uncontrolled and no rigorous double-blinded, randomized, placebo or active-controlled trials exist (6), an evidence-based approach is warranted to strengthen the level of evidence. To revisit relevant evidence and possibly provide a quantitative summary estimate of ASF efficacy, a structured review of relevant literature and a meta-analysis of uncontrolled studies and of cohorts within trials was thus undertaken.

Materials and Methods

Search strategy. A computerized literature search was conducted in the electronic database Medline from inception to January 2012 using various combinations of terms “somatostatin analogs”, “lanreotide”, “octreotide”, “BIM 23014”, “SMS 201995” and “prostatic neoplasm” or “prostate cancer” and was restricted to humans and English language. The procedure was concluded by the perusal of the reference sections of all identified studies or reviews. The main search, as well as screening of titles, abstracts and full-text articles, was completed independently by two reviewers. Any discrepancy was solved unanimously by discussion.

Eligibility of relevant studies (or cohorts within trials). To be eligible, a study had to report data on the efficacy of the ASF in the treatment of castration-resistant prostate cancer independently of study design (concealment, control group) or duration. A study was excluded if i) either an SM-A or an oral glucocorticoid was not used in the combination therapy, ii) a small number (<10) of patients had been recruited, iii) it was retrospective, iv) it reported on duplicate populations or duplication of results from a previous publication could not be excluded, and v) it was not published in full (letters to the editors and abstracts were not eligible), or not published in English.

Data extraction. Information from each study was extracted independently by two reviewers. Emphasis was placed on general characteristics of each study (inclusion and exclusion criteria), details of the intervention and outcomes of interest including responders to treatment, changes in prostate-specific antigen (PSA), performance status, bone pain scores and survival data (overall and prostate cancer-

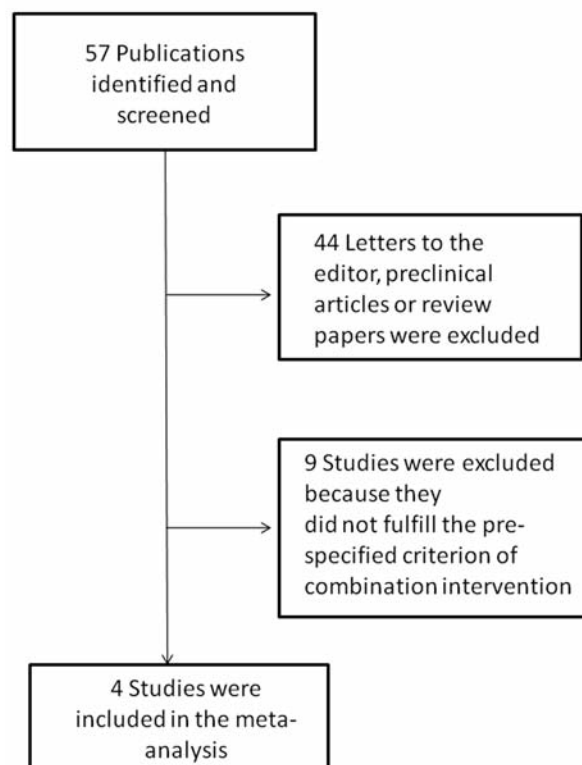


Figure 1. Flow chart summarizing search strategy results.

specific). Since low-dose dexamethasone was used and the SM-A safety profile has been extensively studied in patients with acromegaly, the safety outcomes were not underscored in the present study. When a study included different intervention arms (cohorts from within randomized controlled studies), only outcomes relevant to ASF were considered. SM-A action was considered a class effect.

Statistical analysis. Dichotomous outcomes (responders and non-responders) were treated as probabilities, given that the time interval which they referred to, was similar across studies. The Freeman-Tukey arcsine transformation was applied to stabilize variances (17). Data synthesis was performed using restricted maximum-likelihood random-effects (REML) model and was illustrated in a forest plot. Summary estimates were back-transformed to promote interpretation. Heterogeneity across studies was assessed using the I^2 test (18). Analysis was conducted using appropriate modules (19, 20) in Stata 10.0 for Windows (StataCorp LP, College Station, TX, USA) and in MIX 2.0 Pro software (Bax L: MIX 2.0. Professional software for meta-analysis in Excel. Version 2.0.1.4. BiostatXL, 2011). Paucity of data prevented the evidence synthesis for continuous outcomes.

Results

Search results. The search strategy yielded 57 potentially eligible publications. Forty-four of them were excluded since they were pre-clinical studies, reviews or letters to the editor.

Table I. Major characteristics of the studies (or cohorts within trials) excluded from the evidence synthesis.

Authors/ Year	N, stage	Cohort description	Treatment protocol	PSA, performance and bone pain responses	Survival	Notes
Parmar <i>et al.</i> , 1992	25 D3	All unresponsive to AW and with bone metastasis, mean age 68.7 years	LAN (30 mg <i>i.m.</i> biweekly) or LAN (10 mg <i>i.m.</i> weekly or biweekly) or LAN <i>s.c.</i> 1.5 mg 24 h <i>plus</i> LHRH-a	Partial remission in 8% and stable disease in 12%. Of note, mean duration of treatment 137 days	Median survival: 34 weeks	24% with 50% decline in IGF-1 from baseline
Logothetis <i>et al.</i> , 1994	20 D3	All unresponsive to AW and with bone metastasis	OCTR (100 mg <i>s.c.</i> every 8 h for 6 weeks)	No patients with objective evidence of tumor regression, objective evidence of progression in 5.6 weeks. 70% reported subjective pain relief.	NR	Following progression, SC was instituted
Figg <i>et al.</i> , 1995	25 D3	22 unresponsive to AW, all with bone metastasis, mean age 68.1 years	LAN 4, 7, 10, 13, 18, 24 mg continuous <i>i.v.</i> infusion in escalating doses every 28 days	No clinical response, PSA level increased by 35% in the subset of 22 patients	NR	IGF-1 decline by 41%, no major SE [§] reported in the cohort
Maulard <i>et al.</i> , 1995	30 D3	All unresponsive to AW, mean age 71 years, 60% prior radiotherapy	LAN 30 mg <i>i.m.</i> weekly	PSA decline over 50% from baseline in 20%. Bone pain and performance status improvement in 35% and 40%	1-year global survival rate 72%	No major SE [§] reported in the cohort
Vainas <i>et al.</i> [#] , 1997	14 D2	Mean age 68 years, six without any previous hormonal treatment	OCTR (0.2 mg twice daily <i>s.c.</i> for 12 months) <i>plus</i> CAB	42.8% were considered responders (21.4% were from the hormonally naive subgroup); better quality of life reported	18.5 months in responders	Mild toxicity
Koutsilieris <i>et al.</i> , 1999	4 D3	Aged 64, 71, 70 years, when reported	LAN 30 mg <i>i.m.</i> weekly plus DEX 4 mg PO daily plus triptorelin 3.75 mg 28 days or CAB (1 patient)	Preliminary reports of a significant PSA decline and an improvement in performance status	NR	Presented as four separate case studies
Berruti <i>et al.</i> , 2001	9 D3	Median age 73 years, all with bone metastasis	LAN 30 mg <i>i.m.</i> every 14 days for two months <i>plus</i> androgen deprivation therapy	No change in PSA levels. No bone pain improvement, worsening of performance in 30%	NR	CgA levels decreased, LAN well- tolerated
Di Silveiro <i>et al.</i> , 2003	10 D3	All with bone metastasis and unresponsive to AW	LAN 73.9 mg <i>i.m.</i> monthly plus ethinyloestradiol 1 mg p.o. daily	PR: 90%, CR: 30%. Significant and durable improvement in BPS and performance status	Median PFS: 18.5 months	CgA levels decreased

AW: Anti-androgen withdrawal, BPS: bone pain score, CAB: complete androgen blockade, CgA: chromogranin A, CR: complete response, defined as PSA <4 ng/ml, IGF-1: insulin-like growth factor-1, *i.m.*: intra-muscular, *i.v.*: intra-venously, LAN: lanreotide, LHRH-a: luteinizing-hormone releasing-hormone analog, N: cohort size, NR: not reported, OCTR: octreotide acetate, PFS: progression-free survival, PO: *per os*, PR: partial response, defined as 50% decline from baseline, documented in at least two consecutive assessments, PSA: prostate-specific antigen, SC: salvage chemotherapy, *s.c.*: subcutaneously, SE: side-effects. [§]Defined as such if required hospitalization. [#]Cohort within a randomized trial, outcomes reported refer only to that cohort.

Nine publications were excluded as not fulfilling the pre-specified criterion of the combination intervention (ASF) (21-28) and one study because of the small study size (15). The remaining four studies (29-32) did fulfill the pre-specified inclusion criteria and were used for the evidence synthesis. A flow chart summarizing search strategy results is presented in Figure 1.

Overview of the studies excluded from the meta-analysis. The studies excluded from the evidence synthesis are summarized in Table I. In brief, these nine studies were published between 1992 to 2010 and reported data on 150 patients with prostate cancer (125 with D3 stage prostate cancer) who underwent treatment with lanreotide or octreotide at various dosage schemes or administration

Table II. Major characteristics of the studies (or cohorts within trials) included in evidence synthesis.

Author, Year	N, stage, exclusion	Cohort description	Treatment protocol	PSA response	Performance, bone pain	Survival	Other
Koutsilieris <i>et al.</i> , 2001	11 D3 LE <3 months and/or other malignancy	All patients unresponsive to AW and SC and with >6 mt foci, median age 69 years	LAN (30 mg <i>i.m.</i> weekly) plus DEX (4 mg PO daily, tapered down by half per month to 1 mg) plus triptorelin 3.75 mg per 28 days	(Within 6 months): PR: 72.7% CR: 18.2%	All patients improved their ECOG score and BPS, return to baseline ECOG in 45.5%	Median PFS: 7 months, median overall survival: 18 months	IGF-1, AP, T, DHEA-S decreased no major SE [§] reported
Koutsilieris <i>et al.</i> , 2004	38 D3, LE <3 months and/or other malignancy	All unresponsive to AW and with >6 mt foci, median age 71 years, 44.7% had received SC and 13.2% radiation	OCTR (20 mg <i>i.m.</i> every 28 days plus DEX (4 mg PO daily, tapered down by half per month to 1 mg) plus continuation of androgen ablation therapy before enrollment ^{§§}	(Within 6 months): PR: 60.5% CR: NR, median time-to-return to baseline: 12 months	Significant improvement in ECOG and BPS at PSA nadir, return to baseline BPS in 44.7%	Median PFS: 7 months, median overall survival: 14 months, median prostate cancer-specific overall survival: 16 months	IGF-1, AP, T, DHEA-S, TRACP-5b decreased, no major SE [§] reported
Dimopoulos <i>et al.</i> , 2004 [#]	18*/D3/prior SC, DES, DEX, SM-a, ES administration	All patients unresponsive to AW with mt foci, mean age 74 years, 17% prior radiotherapy, 28% orchiectomized	LAN (30 mg <i>i.m.</i> every two wk) plus DEX (4 mg PO daily, tapered-down by half/ months to 1 or 0.5 mg) plus triptorelin 3.75 mg/ 28 days to those not orchiectomized	PR: 44% CR: 6%, median time for a PSA response, 9 weeks	Pain score improved in 56% and performance status in 41%	Median overall survival: 18 months, median time to progression 4 months	No major SE [§] reported in the cohort
Mitsiades <i>et al.</i> , 2006 [#]	20 D3, LE <3 months and/or other malignancy	All patients unresponsive to AW and SC and with >6 mt foci, mean age 72.3 years, 20% prior radiation	OCTR (20 mg <i>i.m.</i> every 28 d plus DEX (4 mg PO daily, tapered-down by half per month to 1 mg) plus ZOL (4 mg every 4 weeks) plus continuation of androgen ablation therapy before enrollment ^{§§}	PR: 65% CR: NR	All had a sustained improvement in their BPS; significant improvement in ECOG at PSA nadir	Median PFS: 7 months, median prostate cancer-specific overall survival: 14 months	No major SE [§] reported in the cohort

AP: Alkaline phosphatase, AW: anti-androgen withdrawal, BPS: bone pain score, CAB: complete androgen blockade, CgA: chromogranin A, CR: complete response, defined as PSA <4 ng/ml, DES: diethylstilbestrol, DEX: dexamethasone, DHEA-S: dehydroepiandrosterone sulfate, ECOG: Eastern Cooperative Oncology Group, ES: estramustine, IGF-1: insulin-like growth factor 1, *i.m.*: intra-muscular, LAN: lanreotide, LE: life expectancy, LHRH-a: luteinizing-hormone releasing-hormone analog, N: cohort size, NR: not reported, OCTR: octreotide acetate, PFS: progression-free survival, PO: *per os*, PR: partial response, defined as 50% decline from baseline, documented in at least two consecutive assessments, PSA: prostate-specific antigen, SC: salvage chemotherapy, SE: side-effects, SM-a: somatostatin analogs, T: testosterone, TRACP-5b: tartrate-resistant acid phosphatase type 5b, ZOL: Zoledronic acid. [§]Defined as such if required hospitalization. [#]Cohort within a randomized trial, outcomes reported refer only to that cohort. ^{*}Data from 18 out of 20 initially enrolled were finally analyzed and reported. ^{§§}Consisted of LHRH-a monotherapy (13.2%) or CAB (LHRH-a/orchiectomy plus anti-androgen).

routes. The SM-A treatment was accompanied with androgen ablation therapy, in a subset of these studies, as well as with ethinyloestradiol in another. The majority of the studies reported rather poor outcomes with respect to PSA decline, whereas rather better outcomes with respect

to bone pain and performance status. In general, these studies were open-label, uncontrolled, preliminary and of a methodological quality which is vulnerable to bias. Of note, the studies were heterogeneous and thus not comparable.

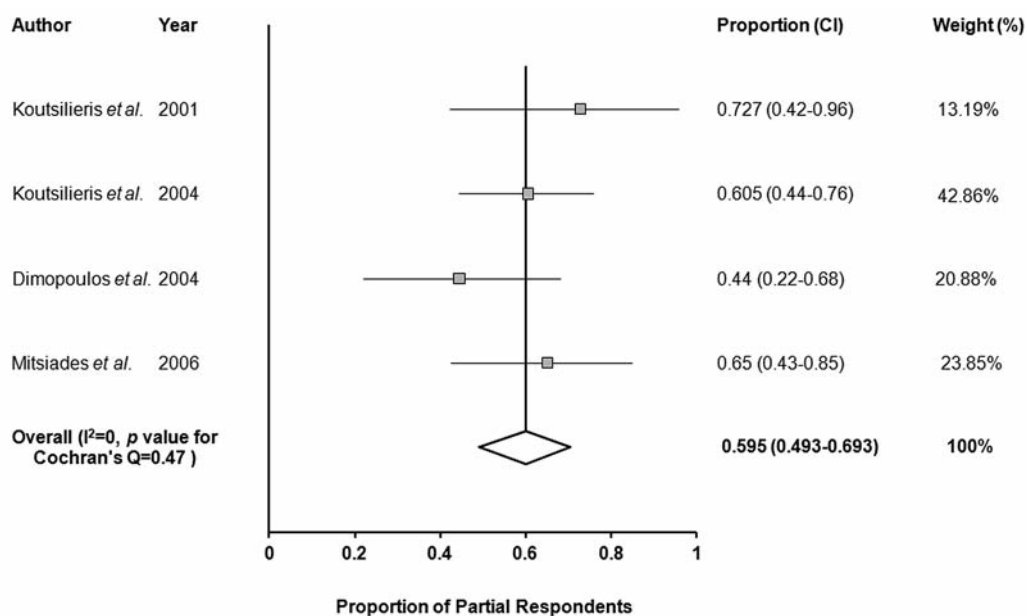


Figure 2. Probability of partial response to antisurvival factor therapy (ASF) in patients with androgen ablation-refractory prostate cancer. Forest plot after Freeman-Tukey arcsine transformation. Footnote: Partial response defined as > 50 % decline in the prostate-specific antigen (PSA) from baseline. CIs: Confidence intervals, PSA: prostate-specific antigen.

Overview of the studies included in the evidence synthesis. The studies included in the evidence synthesis are summarized in Table II. In brief, the four studies were published between 2001 to 2006 and reported data on 87 patients with D3 stage prostate cancer, all of whom had been found to be unresponsive to anti-androgen withdrawal. The combination treatment consisted of SM-A, oral glucocorticoid and androgen ablation therapy, which was also accompanied with zoledronate in one of the studies (31). Lanreotide (30 mg i.m. weekly or biweekly) was used as the SM-A in two of the studies (29, 32), whereas octreotide (20 mg i.m. every 28 days) was used in the other two (30, 31). Dexamethasone was the only oral glucocorticoid used, at a dose of 4 mg *per os* (p.o.), tapered-down by half per month to a dose of 1 or 0.5 mg daily. Either triptorelin or the androgen ablation therapy utilized before enrollment were used for androgen blockade. In two of the studies, combination treatment was compared to estramustine (32) and zoledronate (31).

In general, data regarding ASF in the management of castration-resistant prostate cancer may be considered as rather encouraging. More specifically, PSA concentrations were significantly and rapidly decreased; the proportion of patients with at least a 50% decrease in PSA concentrations was considerable in all cohorts and this was generally achieved within six months of treatment. Normalization of PSA concentrations was rather infrequent, yet improvements in bone pain scores and performance status were consistently reported, even in relapse or in non-responders. Interestingly, the presence of somatostatin receptors (SSTRs), as detected by octreoscan in

such patients, was not found to be a predictor of the response to ASF treatment while reduction of IGF-1 levels correlated with disease response to ASF therapy (30). Safety and tolerability profiles were also satisfactory in all cohorts. Notably, the active-controlled trials demonstrated a non-inferiority of ASF to estramustine, yet with a more favorable safety profile (32), and a clear superiority to zoledronate (31). On the other hand, sustainability of response was rather unsatisfactory; progression-free survival was consistently estimated at 7 months and median overall survival ranged from 14 to 18 months. Notably, progression-free survival and overall survival for other ASF therapies appeared not to be significantly different as compared with those of the current standard chemotherapy.

Meta-analysis. To gain a measure of the magnitude of effect, data regarding the probability of partial response (defined as at least a 50% decrease from baseline PSA concentrations was noted) were analyzed across studies and were pooled using a REML random-effects model. The probability of a partial response (within six months) was estimated at 59.5% and 95% lower and upper confidence intervals were estimated to be 49.3% and 69.3%, respectively (Figure 2). No evidence of heterogeneity was noted (I^2 0%).

Discussion

Androgen ablation therapy in the form of medical or surgical castration almost always offers an objective clinical response

in patients with prostate cancer dissemination in the skeleton, however, the development of castration resistance signals a poor median survival for such patients. Currently, the standard salvage chemotherapy, namely docetaxel plus prednisone, has been shown to offer better clinical responses than mitoxantrone plus prednisone with an overall median progression-free survival of 6 months and median overall survival of 18 months (9, 10). In previous studies, SM-As were administered in advanced prostate cancer, targeting mainly the activation of the SSTRs on prostate cancer cells (the SM-As used acted *via* SSTR-2 and SSTR-5), thus blocking the proliferation/survival of prostate cancer cells. However, these therapies had generally achieved modest, if any, clinical responses (23, 24).

In marked contrast to previous clinical applications of SM-A, the ASF concept includes SM-A administration aiming at the suppression of GH-dependent liver-derived IGF-1 production. This effective indirect mode of therapeutic action for SM-A is corroborated by the analysis of the bone octreotide-scintigraphy studies in patients with castration-resistant prostate cancer, which documented that only a minority (10%) of patients with stage D3 disease presented with positive bone octreoscans (indicating presence of SSTRs in bones) and that most of such patients did not respond to ASF therapy (30). In contrast, the vast majority (68.5%) of those with negative bone octreotide-scintigraphies did respond to ASF manipulation, thus further supporting the notion that the antitumor activity of SM-A is not mediated by SSTR-2 and SSTR-5 binding on prostate cancer cells (30). Nevertheless, new cytotoxic SM-As, which can target other SSTR subtypes (*e.g.* SSTR-1, SSTR-3 and SSTR-4) might exert both direct (through binding to SSTRs on tumor cells) and indirect (through suppression of IGF-1) antitumor actions (16).

The ASF concept includes also the use of oral glucocorticoids, which takes advantage of both the direct action of these compounds on prostate cancer cells (13) and the down-regulation of the expression of osteoblast-derived survival factors (12) and of uPA, which is a local regulator of both IGF-1 and TGF-1 bioavailability in the skeleton (12-14). Notably, glucocorticoids are commonly used as supportive treatment in the context of salvage chemotherapy, and the significant actions of these drugs on prostate cancer biology and on bone metastasis microenvironment is frequently neglected (14).

The present study revisited the evidence regarding the efficacy of ASF manipulation for the treatment of castration-resistant prostate cancer. Overall, it appears that the ASF may be a safe alternative to standard therapy, since it induces a partial remission in at least a half of the patients, which lasts for at least 6 months. In addition, it appears that this partial response is consistently accompanied by a significant improvement in bone pain, performance status and, thus, quality of life. Regrettably, the response noted does not persist over time (median progression-free survival of seven months and median overall survival of 16 months) in the majority of

patients. This, however, is very similar to the clinical response achieved by the standard salvage chemotherapy, with the added benefit of a very positive side-effect record observed with the ASF regimens. Recently, the ASF manipulation has shown a synergistic effect with standard chemotherapy, increasing significantly the anticancer actions of docetaxel in the TRAMP-C1 prostate cancer model for bone metastasis (33).

The findings of the present study should be interpreted in the context of its limitations. More specifically, it should be noted that primary studies included in the meta-analysis were either of before-and-after design, or cohorts within controlled trials treated as the former (before-and-after design). In other words, they confer a moderate level of evidence ranging from 2c to 4 (<http://www.cebm.net>). This also means that even the effects of time are not controlled for, which further undermines the validity of results. In addition, the lack of a control may have resulted in overestimation of the effectiveness of the intervention (Hawthorne effect, the non-specific beneficial effect on performance of taking part in research) (34), which needs to be taken into account in the interpretation of the results. Finally, the paucity of evidence precluded the analysis of other outcomes of interest and further rendered our estimates more vulnerable to bias.

Taking the above into consideration, it could be argued that sufficient evidence suggests that patients with androgen ablation-refractory (D3) prostate cancer may have a significant probability of partial remission when on ASF. Hard evidence on that and on the comparative efficacy of ASF manipulations to standard chemotherapy, as well as novel treatments are still lacking; however, at least bibliographically, these treatments do not appear to be superior in terms of PSA response or survival benefit and safety profile.

Conflict of Interest

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