Management and challenges of corticosteroid therapy in men with metastatic castrate-resistant prostate cancer
T. B. Dorff* & E. D. Crawford

Division of Cancer and Blood Diseases, Department of Medicine, USC Norris Comprehensive Cancer Center, Los Angeles; Section of Urologic Oncology, Division of Urology, University of Colorado, Denver, USA

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Extensive clinical development in metastatic castrate-resistant prostate cancer (mCRPC) has led to the introduction of three new agents in little more than a year, with more on the horizon. With the exception of autologous cellular immunotherapy, all of the agents approved by the US Food and Drug Administration for the treatment of mCRPC are approved for use in combination with corticosteroids. Corticosteroids play a crucial role in the management of men with mCRPC, but the availability of multiple lines of therapy that include corticosteroids raises potential toxicity considerations. In addition, the immunosuppressive effects of corticosteroids may alter the efficacy of immunotherapies.

The recent increase in treatment options with different mechanisms of action raises the importance of understanding how corticosteroids are used and the implications of such use on treatment selection and sequencing. A number of corticosteroids with varied potencies are used in general medical practice at varying doses. The differences in potency, dose, and disease settings in which corticosteroids are used complicate the ability to fully understand the impact that any one corticosteroid can have, such as prednisone in prostate cancer. This article reviews the published literature on corticosteroid use in advanced cancer, focusing on their role in mCRPC.

Key words: corticosteroid, immunotherapy, metastatic castrate-resistant prostate cancer, systemic therapy, treatment sequencing

introduction

Since 2010, there has been a rapid increase in the number of therapies available to men with metastatic castration-resistant prostate cancer, including abiraterone, cabazitaxel, and sipuleucel-T. The first two agents require the concurrent use of corticosteroids, and the third was tested in men who were not receiving any corticosteroids or other immunosuppressive therapy. The increasing complexity of therapeutic options has yielded many questions, especially regarding the impact of using corticosteroids for increasingly long periods of time and how corticosteroids affect sequencing of the new treatment regimens. In an effort to help inform clinical decision making, we undertook a review of the risks, benefits, and treatment implications of corticosteroid use in advanced prostate cancer. We searched PubMed using the following terms: corticosteroids, glucocorticoids, prednisone, prostate cancer, toxicity (in general, but also by specific adverse events (AEs): adrenal insufficiency, osteoporosis, osteonecrosis, hypertension, hyperglycemia, cataract, glaucoma, insomnia, atrophy, myopathy, infection).

corticosteroids in cancer

Corticosteroids are commonly used in the treatment of cancer, primarily owing to their anti-inflammatory activities [1]. Corticosteroids can mimic endogenous cortisol or mineralocorticoids and thus activate the glucocorticoid receptor to up-regulate expression of anti-inflammatory proteins and down-regulate expression of proinflammatory proteins [2]. In prostate cancer, corticosteroids also may have a direct effect on tumor-induced pain [3] that is secondary to the propensity of prostate cancer to metastasize to the osseous skeleton. Thus, in the treatment of prostate cancer, corticosteroids are used both to counteract toxic effects associated with specific cancer therapeutics and to manage tumor-related symptoms.

In the management of tumor-related symptoms, corticosteroids may be used to help mitigate metastatic bone pain and improve appetite to reduce weight loss. In a randomized, double-blind trial in terminally ill patients with solid tumors (n = 40), daily methylprednisolone (MP, 16 mg b.i.d.) was shown to reduce mean pain intensity (visual analog...
score 36.8 ± 14 in the MP group versus 57.7 ± 15 in the placebo group, P < 0.01), analgesic consumption (57% of MP patients versus 14% of placebo patients, n = 28), and depression (71% of MP patients versus 13% of placebo patients, n = 31), as well as to improve appetite (77% of MP patients versus 10% placebo patients, n = 31) and daily activity (61% of MP patients versus 16% of placebo patients, n = 31), compared with patients who received a placebo control [4]. Dexamethasone (0.75 or 1.5 mg four times daily) was also shown to significantly improve appetite (P < 0.05) and trended toward a significant improvement in strength (P < 0.07) compared with placebo in patients with advanced gastrointestinal cancer (n = 116) [5]. In a prospective study in patients with symptomatic metastatic castrate-resistant prostate cancer (mCRPC), pain relief and improvement in overall well-being were attained in more than one-third of patients treated with prednisone alone [3]. In patients without castrate levels of testosterone at baseline, prednisone (7.5–10 mg daily, split doses) reduced serum testosterone to castrate levels in 78% of patients. Furthermore, there was a correlation between improvement in cancer symptoms and suppression or low baseline serum levels of androstenedione and/or dehydroepiandrosterone. These results support the hypothesis that the mechanism of action of prednisone may be due, in part, to the mediation of androgen production by the adrenal gland. In addition, corticosteroids help prevent the syndrome of secondary mineralocorticoid excess and may help maximize the efficacy of CYP17 inhibitors, such as abiraterone acetate (Zytiga®; Janssen Biotech, Inc.; Horsham, PA) [6].

Table 1 provides an overview of corticosteroids commonly used in cancer treatment and their relative potency [7].

### side-effects of corticosteroids

Although corticosteroids are used in prostate cancer and other malignancies to help manage treatment-related toxic effects and disease-related morbidities, corticosteroids are not without their own side-effects. There are limited published data on corticosteroid-related AEs specific to prostate cancer. This article provides an overview of key corticosteroid-related toxic effects as reported in studies conducted with various corticosteroids, at various doses, and for different durations and various malignancies. In some of these studies, daily doses may be much higher than those typically used in mCRPC. However, the total dose exposure is also an important consideration, as high total doses of corticosteroids can be much higher than those typically used in mCRPC who may receive multiple lines of therapy that include corticosteroids.

Corticosteroids have been shown to cause edema, hypertension, weight gain, hyperglycemia/steroid-induced diabetes, posterior subcapsular cataracts, and glaucoma, depending on disease state, dose, and duration of therapy. In a retrospective analysis of 59 patients with primary or metastatic brain tumors or epidural spinal cord compression [8], the use of dexamethasone at various doses and durations of therapy resulted in 51% of patients developing one or more AEs, including hyperglycemia (19%), infection (22%), and myopathy (19%). In addition, 19% of patients required hospitalization for diagnosis and/or management of steroid complications. Specifically, in patients who received dexamethasone for >3 weeks, the incidence of a corticosteroid-related toxicity was 76% compared with only 5% of patients treated for <3 weeks. Seventy-five percent of patients who received a total dexamethasone dose of >400 mg had a corticosteroid-related toxicity compared with only 13% of patients who received a total dexamethasone dose of <400 mg [8]. Although dexamethasone is primarily used in mCRPC as a premedication for taxane-based chemotherapy to minimize acute hypersensitivity reactions and fluid retention, it adds to the total corticosteroid exposure of these patients [11, 12]. In a prospective study in 373 patients with advanced solid tumors admitted to a single hospice institution and treated with corticosteroids (starting doses of 10–30 mg/day of prednisolone, or 4–16 mg/day of dexamethasone) [13], the most common AEs associated with corticosteroid use were oral candidiasis (26% prednisolone, 37% dexamethasone), edema (18% prednisolone, 21% dexamethasone), cushingoid facies (15% prednisolone, 21% dexamethasone), dyspepsia (8% prednisolone, 9% dexamethasone), and weight gain (4% prednisolone, 5% dexamethasone). See Table 2 for a summary of AEs associated with corticosteroid use [8, 10, 13–22].

Owing to the mechanism of the action of corticosteroids and their associated side-effects, caution may be warranted when using these agents in patients with specific comorbidities. The use of corticosteroids in men with prostate cancer who have completed multiple years of androgen deprivation therapy (ADT) should be considered with caution, as this patient population may be at an elevated risk of cardiovascular and metabolic diseases that could be exacerbated further by the use of corticosteroids [23]. Specifically, ADT has been shown in prospective studies to cause decreased lean muscle mass, increased fat mass, weight gain, increased cholesterol and triglycerides, insulin resistance, and loss of bone mineral density [23]. Most of these effects were observed after 1 year of therapy. Together, these effects may result in increased risk of cardiovascular disease among men following long-term treatment with ADT. This risk is supported by data from two population-based studies showing an association between cardiovascular disease and ADT. The first study showed a 16% increased risk of coronary heart disease, an 11% increase in myocardial infarction, and a 16% increase in sudden cardiac death or life-threatening ventricular arrhythmia [24]. The second study showed a 20% increased risk of serious cardiovascular morbidity [25].
on 14 July 2018

Hyperglycemia/diabetes [8, 14, 15*, 16*] Low-dose dexamethasone (0.5–2 mg/day)*; low-dose prednisone (10 mg/day)
Infection [8, 10, 13] Fungal infections
Myopathy/muscle loss [8, 16*] Low-dose prednisone (10 mg/day)*
Insomnia [17, 18]
Osteoporosis/avascular bone necrosis [19–21]
Edema [13, 16] Low-dose prednisone (10 mg/day)*
Weight gain [13]
Dyspnea [13, 16*] Low-dose prednisone (10 mg/day)*
Cushingoid facies [13]
Posterior subcapsular cataracts [15*, 22] Low-dose dexamethasone (0.5–2 mg/day)*

Notes: Choice of corticosteroid, as well as dose, duration, and therapeutic indication varies for each study. AEs shown to be attributable to corticosteroid use in mCRPC are denoted with an asterisk, with steroid type and dose noted; corresponding studies are also denoted with an asterisk.
AE, adverse events; mCRPC, metastatic castration-resistant prostate cancer.

The importance of understanding specific corticosteroid-related toxic effects that may have increased significance in men with prostate cancer is discussed in the following sections.

**osteoarthritis**

Osteoporosis caused by an abnormal handling of calcium cations is a widely documented side-effect of glucocorticoid treatment [19, 26, 27]. Low doses of prednisone (6 mg/day) for as little as 6 months may increase the rate of osteoporotic fractures within 1 year [19]. Avascular bone necrosis also may occur with prolonged administration of corticosteroids [20]. In a review of 194 patients who received a renal transplant and posttransplant prednisone (mean 15.9 mg/day), 21% of patients developed avascular bone necrosis (mean 1.5 years post-surgery) [20]. Additionally, various reports have suggested that the incidence of bone necrosis may be correlated with the mean daily dose of corticosteroids during the first month posttransplantation [20]. Case reports of such necroses have been reported with the use of high-dose dexamethasone (total dose 172–216 mg) for 3–6 weeks duration in patients with neurologic disorders [21] and for as little as 4–6 weeks in patients receiving corticosteroids as part of a combination chemotherapy regimen for malignant lymphoma (total dose, 500 mg–9 g) [28]. The frequent use of bisphosphonates or receptor activator of nuclear factor kappa-B ligand inhibitors in prostate cancer patients may reduce the risk of such bone necrosis.

**hyperglycemia**

Corticosteroid-related hyperglycemia has been found to occur with high frequency in patients treated with corticosteroids. A retrospective review of hospitalized patients treated in a single institution found that 64% of patients (disease indications not specified) treated with high-dose corticosteroids (≥240 mg/day of prednisone or equivalent) had at least one episode of hyperglycemia (defined as a blood glucose level ≥200 mg/dl), and 52% of patients had multiple episodes [14]. Elevated blood glucose became apparent in patients receiving as few as 5 days of corticosteroid therapy, and longer duration of corticosteroid therapy was associated with multiple episodes of hyperglycemia.

**loss of muscle mass**

Loss of muscle mass has also been described, occurring in 10.6% of patients with primary brain tumors who were treated with dexamethasone (median total dose, 900 mg) for ≥2 weeks [9]. Although the doses of dexamethasone used here are substantially higher than those used in mCRPC, this issue may have relevance in prostate cancer since loss of muscle and lean body mass have been shown to occur in men treated with ADT [29].

**insomnia**

Insomnia is another common side-effect of corticosteroids. In a study in patients with various solid tumors, moderate-to-severe insomnia occurred within the first week in 45% of patients treated with daily oral dexamethasone (dose not specified) as prophylaxis for delayed chemotherapy-induced nausea and vomiting [17, 18].

**immune suppression**

Corticosteroids have been shown to affect T-cells, leading to reduced function of the immune system [30]. Owing to the immunosuppressive effects of corticosteroids, patients may be at increased risk for infection [10]. In a retrospective review of 71 clinical trials, patients treated with corticosteroids had an associated 1.6 relative risk of infectious complications compared with patients not receiving corticosteroids, although low doses of prednisone (<10 mg/day or total dose <700 mg) did not significantly increase the infection rate [10].

High daily doses, greater than those used in mCRPC, are most associated with increased immunosuppressive effects and risk of infection. Currently approved corticosteroid-containing drug regimens for the treatment of mCRPC recommend 10 mg of prednisone daily [31]. However, it is important to note that a high cumulative dose of corticosteroids also carries risk. Therefore, the low daily doses of corticosteroids used in mCRPC for a prolonged duration also may put these patients at risk of infection.

**corticosteroid use in mCRPC**

Multiple treatment approaches are available for the treatment of mCRPC—secondary hormonal manipulation (e.g. androgen biosynthesis inhibitors), immunotherapy (i.e. autologous cellular immunotherapy), and chemotherapy (e.g. taxanes). Although effective, chemotherapeutics and secondary hormonal agents are associated with certain side-effects that can be ameliorated by concomitant use of corticosteroids. In particular, chemotherapeutics can cause nausea, vomiting, edema, and hypersensitivity reactions, all of which can be
managed with corticosteroids. In addition to premedication with dexamethasone used to reduce the side-effects of docetaxel, it is routine to prescribe prednisone 5 mg twice daily throughout the course of docetaxel chemotherapy for prostate cancer patients. The value of adding prednisone to taxane-based chemotherapy in prostate cancer appears to be primarily related to side-effect management versus response. PSA response rates (defined as >50% PSA reduction) associated with docetaxel treatment with and without the addition of prednisone have been relatively consistent. Two separate phase II trials of weekly docetaxel at 36 mg/m² without prednisone yielded PSA response rates of 41%–46% [32, 33]. These results were similar to findings from two randomized trials that compared docetaxel alone (30 mg/m² weekly) with docetaxel plus either calcitriol or thalidomide without prednisone [34, 35]. In these studies, PSA response rates were 37%–49%. Similarly, a PSA response rate of 45%–48% was seen in the phase III TAX327 study, which paired docetaxel (30 mg/m² weekly or 75 mg/m² every 3 weeks) with prednisone 5 mg p.o. b.i.d., [36]. However, in TAX 327, fatigue was experienced by 49% with 5% grade 3/4 compared with 81% with 16% grade 3/4 in the control arm of the ASCENT trial (without prednisone) [34, 36]. There was also less peripheral edema reported in TAX327 than in the ASCENT trial (12% versus 37%). Hyperglycemia, which could be worsened with the addition of prednisone, was not reported for TAX327.

Secondary hormonal agents, such as ketoconazole and abiraterone acetate, act through the disruption of androgen biosynthesis pathways in a dose- and time-dependent manner, resulting in a reduction in cortisol and mineralocorticoids, which may lead to adrenal insufficiency or adrenal crisis [37]. Corticosteroids are used concomitantly to prevent these conditions, which often manifest as hyponatremia, hyperkalemia, hypotension, lethargy, depression, and malaise. Abiraterone acetate, which is approved for the treatment of advanced prostate cancer Patients may receive one or more of these therapies over the course of their disease management, which may further increase their total corticosteroid exposure.

Corticosteroids. In fact, corticosteroids may actually interfere with the treatment effect of immunotherapeutic agents given their immunosuppressive activity [30, 38, 39]. For this reason, recent clinical trials of immunotherapies in mCRPC (BNIT-PRV-301, NCT01322490, NCT00065442) have prohibited corticosteroid use during the course of immunotherapy.

duration-of-use considerations in prostate cancer

The onset of AEs associated with corticosteroid use can occur within a few days to a few weeks of treatment, depending on the dose administered. In patients with CRPC, treatment with corticosteroids is often at a low dose, but for a prolonged duration of time. Table 3 summarizes the average total dose of corticosteroids associated with regimens approved by the US Food and Drug Administration (FDA) for the treatment of patients with mCRPC [40–43]. The total corticosteroid exposure associated with each of these regimens may put patients at risk of developing corticosteroid-related AEs. Patients may receive one or more of these therapies over the course of their disease management, which may further increase their total corticosteroid exposure.

Secondary hormone manipulation with ketoconazole may be given for several months in combination with low-dose hydrocortisone (40 mg/day divided dose) or prednisone (5 mg b.i.d.) [40]. In patients with mCRPC, taxane chemotherapy plus prednisone also may be administered for several months, depending on the line of therapy. In the phase III TAX327 trial, which compared docetaxel plus prednisone (5 mg b.i.d.) with mitoxantrone plus prednisone (5 mg b.i.d.) as the first-line therapy for mCRPC, the average number of cycles administered of docetaxel (q3w) plus prednisone was 9.5, which amounts to 6.5 months of therapy [36]. In the phase III TROPIC study, which compared cabazitaxel plus prednisone

Table 3. Corticosteroid dosing in common therapeutic regimens for mCRPC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Study</th>
<th>Daily corticosteroid dose</th>
<th>Treatment setting</th>
<th>Median duration of therapy (months)</th>
<th>Total calculated potential prednisone-equivalent dose (mg)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole + hydrocortisone [36]</td>
<td>CALGB 9583</td>
<td>30 mg q.a.m. and 10 mg q.p.m.</td>
<td>mCRPC, chemotherapy naïve</td>
<td>8.6</td>
<td>2580b</td>
</tr>
<tr>
<td>Docetaxel + prednisone [37]</td>
<td>TAX327</td>
<td>5 mg b.i.d.</td>
<td>mCRPC, chemotherapy naïve</td>
<td>6.5</td>
<td>1950</td>
</tr>
<tr>
<td>Cabazitaxel + prednisone [38]</td>
<td>TROPIC</td>
<td>5 mg b.i.d.</td>
<td>mCRPC, docetaxel pretreated</td>
<td>4.1</td>
<td>1230</td>
</tr>
<tr>
<td>Abiraterone + prednisone [39]</td>
<td>COU-AA-301</td>
<td>5 mg b.i.d.</td>
<td>mCRPC, docetaxel pretreated</td>
<td>8.0</td>
<td>2400</td>
</tr>
</tbody>
</table>

mCRPC, metastatic castration-resistant prostate cancer; b.i.d., twice daily; q.p.m., every night.

aTotal calculated potential prednisone-equivalent dose is calculated as daily dose administered per protocol in each study multiplied by the reported median duration of therapy (or median time to progression if duration of therapy not reported). A month was assumed to have 30 days. This calculation represents the potential total dose that may be administered for each regimen; this may differ from actual doses received if patients receive dose reductions or shorter durations of therapy.

b2580 mg of prednisone is roughly equivalent to 10 320 mg of hydrocortisone, based on the relative potencies of the two corticosteroids shown in Table 1 (20 mg of hydrocortisone is equivalent to 5 mg of prednisone).
(5 mg b.i.d.) with mitoxantrone plus prednisone (5 mg b.i.d.) as the second-line therapy for mCRPC, the average number of cycles administered of cabazitaxel plus prednisone was 6, which amounts to 4.1 months of therapy [41]. Alternatively, taxane-refractory mCRPC patients may receive abiraterone plus prednisone (5 mg b.i.d.). Data from the pivotal trial show that the median duration of therapy for abiraterone is 8 months [42]. Treatment of a patient with CRPC may thus require multiple lines of therapy that include a corticosteroid, potentially achieving high levels of total corticosteroid exposure that may put these patients at risk of developing corticosteroid-related AEs. Despite the risk, it is worth noting that in the pivotal trials for docetaxel, cabazitaxel (Jevtana®, Sanofi, U.S., LLC, Bridgewater, New Jersey), and abiraterone acetate, the reported incidence of corticosteroid-related toxic effects was minimal, limited to hypertension and infections [36, 41, 42].

Another concern with long-term utilization of corticosteroids is steroid dependency, largely related to the disruption of the hypothalamic–pituitary–adrenal (HPA) axis during the period of corticosteroid administration (and other concomitant therapy). An abrupt withdrawal of corticosteroids following prolonged use can result in prolonged suppression of the HPA axis (secondary adrenal insufficiency), steroid withdrawal symptoms (e.g. anorexia, nausea, vomiting, weight loss, asthenia, headache, myalgia, arthralgia, postural hypotension, tachycardia, fever, flaky skin, and mood swings), and relapse of the disease (although this is more common in nononcological indications) [43]. In order to prevent the development of corticosteroid withdrawal symptoms, a gradual tapering of corticosteroids may be required. Such dependency is most often seen when patients have been treated with high doses of corticosteroids, but can occur in patients who receive low maintenance doses of corticosteroids for a prolonged duration. While not common in mCRPC, it is important to be aware of the potential for corticosteroid dependency and the possible need for tapered withdrawal if corticosteroid therapy is discontinued. No consensus documents exist to provide guidelines on how to taper the dose of corticosteroids, but one approach in patients who have been on chronic corticosteroids and continue to have underlying disease is to reduce the dose of corticosteroid by 10%–20% per day until a physiologic dose is reached (3.5–5.5 mg/day prednisone), and then to further reduce the dose to half, the physiologic dose over a 2–4-week period, followed by adrenocorticotropic hormone (ACTH) monitoring and complete discontinuation of the corticosteroid once baseline morning serum ACTH and cortisol are at normal levels [43]. In a clinical study with ketoconazole/hydrocortisone in CRPC patients, hydrocortisone was withdrawn over a 3-week period (tapered at a rate of 5 mg every 3 days) [37].

**therapeutic options and the integration of corticosteroids**

Many therapeutic options exist for men whose prostate cancer becomes castrate resistant (Figure 1) [44, 45], and several factors can aid in developing a treatment plan, including the extent of the disease (metastatic or nonmetastatic; visceral or nonvisceral), symptom burden, performance status, comorbid conditions, age, life expectancy, and patient preference. In patients with symptomatic metastatic disease, docetaxel plus prednisone 5 mg b.i.d. is recommended if the patient is able to tolerate the therapy [44, 45]. The recommendation of docetaxel plus prednisone is based on the results of the randomized TAX327 trial, which demonstrated a survival benefit of 2.4 months compared with mitoxantrone plus prednisone [36]. Patients unable to tolerate docetaxel may be treated with mitoxantrone plus prednisone, based on demonstrated pain palliation and time-to-progression benefits [45–47]. For patients who progress on treatment with docetaxel, both cabazitaxel and abiraterone acetate are approved options based on proven prolongation of overall survival [41, 42].

Chemotherapy is not typically recommended for patients with asymptomatic or minimally symptomatic mCRPC [44, 48]. Sipuleucel-T, an autologous cellular immunotherapy, is approved by the FDA and recommended by the National Comprehensive Cancer Network (NCCN) for this patient population, although it has not yet been incorporated into EAU guidelines [45]. Sipuleucel-T was approved based on a statistically significant improvement in overall survival compared with control [25.8 versus 21.7 months, hazard ratio (HR) 0.78; \( P = 0.03 \)] in patients with asymptomatic or minimally symptomatic mCRPC [49].

Other options for patients with asymptomatic or minimally symptomatic mCRPC are observation alone or secondary hormonal manipulation. Observation alone has been used historically in asymptomatic patients, owing to a desire to delay chemotherapy or secondary hormonal manipulation [48]. Secondary hormonal manipulation may include ketoconazole plus hydrocortisone or prednisone; low-dose ketoconazole with or without hydrocortisone (40 mg/day) or prednisone (5 mg b.i.d.); or antiandrogens such as bicalutamide, flutamide, or nilutamide, which do not require corticosteroids. Abiraterone is not currently approved by the FDA for this indication, but it received a category 2B recommendation by the NCCN based on single-arm phase II data [44, 50]. Importantly, ketoconazole, the antiandrogens, and abiraterone have not demonstrated an overall survival benefit in the prechemotherapy mCRPC setting to date, although a randomized phase III trial (COU-AA-302, NCT00887198) of abiraterone plus prednisone versus prednisone alone in chemotherapy-naïve, asymptomatic or minimally symptomatic mCRPC showed a progression-free survival advantage, with overall survival results pending.

With multiple treatment options available, questions arise regarding optimal sequencing. As described previously, secondary hormonal manipulation (i.e. ketoconazole or abiraterone) and chemotherapy require concomitant use of corticosteroids. Given the known immunosuppressive effects of corticosteroids, the phase III IMPACT study required a minimum 28-day washout of all corticosteroids before treatment with sipuleucel-T [49]. Thus, the impact of timing and sequence of steroid-containing regimens relative to therapy with sipuleucel-T remains a clinically relevant, yet largely unanswered, question. Information on prior steroid use was not specifically collected in sipuleucel-T clinical studies, so there are limited data to provide guidance. However, up to 20% of subjects who received sipuleucel-T in the registrational trials...
had been treated with prior chemotherapy, presumably with concomitant steroids, and subset analysis demonstrated that the survival advantage was maintained in this group of patients [49]. Following objective radiographic disease progression in the IMPACT study, 57.2% of subjects treated with sipuleucel-T and 50.3% of subjects receiving control went on to receive docetaxel therapy, again presumably with corticosteroids. Neither use nor timing of subsequent treatment with docetaxel significantly impacted the treatment effect attributable to sipuleucel-T (HR for death 0.78; 95% CI 0.62–0.98; \( P = 0.03 \)) [49]. Since docetaxel therapy could be initiated after \( \sim 14 \) weeks in either arm, these data would suggest that a 14-week period is a sufficient period to wait following sipuleucel-T therapy to avoid any potential detrimental impact of steroid-containing chemotherapeutic regimens on the immune response [49].

Recent preclinical research in prostate cancer has shown that ADT may influence T- and B-cell development through an interaction between testosterone and the thymus and bone marrow as a consequence of androgen receptors expressed in thymocytes, thymic stromal and epithelial cells, immature B-cells, and bone marrow stromal cells [51]. These studies have shown that androgen deprivation results in increased thymopoiesis, which can increase the diversity of the T-cell repertoire, suggesting that ADT may improve the efficacy of immunotherapies. Further studies are needed to explore whether concurrent or sequential use of existing and emerging hormone and immune therapies results in the best outcomes.

### conclusions

Corticosteroids are an important component of treatment of mCRPC, owing to their ability to manage toxic effects associated with adrenal synthesis inhibitors and chemotherapeutics, ameliorate prostate cancer-related symptoms, and potentially help maximize the efficacy of CYP17 inhibitors. However, corticosteroids are also associated with toxic effects themselves, which may require close patient monitoring and proper tapering if corticosteroid use needs to be discontinued. Additionally, the immunosuppressive action of corticosteroids may interfere with the effectiveness of immunotherapy, such as sipuleucel-T. Further studies are needed to clarify this potential effect. These factors necessitate careful consideration of treatment sequencing over the course of therapy for patients with mCRPC. Based on the available data, the following recommendations for managing corticosteroids in mCRPC patients can reasonably be put forth:

- Until additional data are generated, concomitant corticosteroids should be used in the dose and schedule used in clinical trials leading to approval of agents, including docetaxel, cabazitaxel, and abiraterone.
- Men with mCRPC on a therapy that requires concomitant steroid use should be monitored for steroid toxic effects, including thrush and hyperglycemia. The presence of such toxic effects may necessitate dose adjustment, which would

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**Figure 1.** Potential sequencing options for metastatic castration-resistant prostate cancer (mCRPC). HT, hormone therapy. The European Association of Urology further notes in their 2012 Guidelines on Prostate Cancer that Radium223 may be a potential option for men with symptomatic mCRPC who are ineligible for or progressing to docetaxel [45]. Reproduced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.3.2012. © 2012 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, visit http://www.nccn.org.
Corticosteroids are unlikely to diminish the effect of sipuleucel-T when initiated >14 weeks after treatment completion. Earlier administration should be evaluated.

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**references**

Controversies and challenges regarding the impact of radiation therapy on survival

C. Chargari1,4, J. -C. Soria2 & E. Deutsch1,3*

1INSERM 10-30, Molecular Radiotherapy, Université Paris XI, Institut Gustave Roussy, Villejuif; 2Department of Medical Oncology, Institut Gustave Roussy, Villejuif; 3Department of Radiation Oncology, Institut Gustave Roussy, Villejuif; 4Department of Radiation Oncology, Hôpital d’Instruction des Armées du Val-de-Grâce, Paris, France

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Novel irradiation techniques and radiosensitizing strategies revealed their interest for improving the antitumor efficacy of radiation therapy (RT) and thus for reducing locoregional failures. We analyzed the relevance of these strategies with regard to their impact on survival. The examples of the targeted molecular agent cetuximab and dose intensification in head and neck and lung cancer show that this benefit in local control is associated with a survival benefit. Large meta-analyses comparing sequential versus concurrent chemoradiation have also highlighted that improvement in local control is a major contributor to the survival benefit observed in chemoradiation trials. This close link between local control and survival encourages us to pursue our efforts to further improve the efficacy of RT. In some cases, the survival benefit afforded by radiotherapy is however marginal. The better understanding of the impact of local control on overall survival might allow optimization of clinical trials designs.

Key words: chemotherapy, local control, radiation therapy, survival, targeted agent

introduction

About 50% of cancer patients receive radiation therapy (RT) during the course of their disease. RT modalities have drastically evolved over the past few years. New technologies have allowed dose escalation strategies while minimizing toxic effect [1]. In parallel, greater knowledge of tumor biology has led to the identification of numerous molecular targets for radiosensitization. These costly developments could be used to decrease locoregional failures. However, faced with today’s economic crisis, the relevance of these strategies should be analyzed with regard to their impact on survival. The most