8. Disseminated prostate cancer

From the \textit{anatomopathological} point of view, a patient with disseminated prostate cancer is one with the confirmed presence of prostate adenocarcinoma with lymphatic invasion (N1) and/or metastasis (M1) and/or a primary fixed tumour or one that invades adjacent structures other than the seminal vesicles (pT4).

The patient with \textit{clinically} disseminated prostate cancer spread corresponds to a stage N1, M1 or cT4.

8.1 Hormone therapy

Questions to answer:

• In patients with disseminated prostate cancer, what is the safest and most effective treatment: complete androgen blockade or (surgical or chemical) castration?

• In patients with disseminated prostate cancer (lymph node affectation and/or metastasis), what is the safest and most effective treatment: immediate or delayed hormone treatment?

• In patients with disseminated prostate cancer, what is the safest and most effective hormone treatment: continuous or intermittent? And using what treatment guidelines?

• In patients with prostate cancer where the first line hormone treatment (androgen suppression, complete androgen blockade) has failed and the PSA has begun to rise, what is the safest and most effective: continue with the following lines of hormone

8.1.1 Complete androgen blockade vs castration

The goals of treatment in men with disseminated prostate cancer include prolonging life, preventing or delaying the symptoms caused by the disease, improving the quality of life and reducing the morbidity associated with treatment\textsuperscript{16,217}.

When hormone treatment is suggested in these patients, there are different options. Androgen suppression or ablation (castration) can be done with LHRH agonists (luteinising hormone-releasing hormone) or surgery (orchiectomy). Both options are considered to have comparable survival rates and side effects. The use of chemical castration, compared to surgery, has both advantages (such as the possibility of intermittent application) and disadvantages (greater cost, lack of adherence to treatment)\textsuperscript{16}.

Another possibility of hormonal treatment in these patients is antiandrogens, which may be non-steroidal (flutamide, nilutamide, bicalutamide) or steroidal (cyproterone acetate)\textsuperscript{4,16}.
There is a tendency to obtain better overall survival results with antiandrogen castration. Both treatments have different toxicity profiles: gynecomastia is more common with non-steroidal antiandrogens, while hot flushes and decreased sexual function are more likely with androgen deprivation. The dropout rate is similar for agonists and LHRH antiandrogens.16

When LHRH agonists are administered in monotherapy, the patient also receives a short period of antiandrogen treatment to prevent the "flare phenomenon". If this is not done, the chemical castration provokes a regenerative blast reaction in bone metastatic lesions, with at times new lesions appearing.221

LHRH analogues can also be administered in combination with anti-androgen treatment, which is called "complete androgen blockade (CAB)." This alternative therapy can be applied as an initial hormone guidance or exclusively after failing with castration treatment.4,16

RCT (1++) reviews Different reviews conclude that CAB provides an improvement (of about 3%) in survival at 5 years when compared with castration. It seems that this benefit occurs only in patients taking non-steroidal antiandrogens.223-226

RCT (1+) review When estimating the CAB effect of using bicalutamide vs castration, the global mortality hazard ratio showed a small statistically significant difference in favour of the blockade (HR = 0.8 [95% CI: 0.66-0.98]).

RCT (1++) reviews Cancer-specific survival was better with CAB than with orchietomy, except when the androgen blockade was cyproterone acetate.223,226

RCT (1++) reviews In the Schmitt et al review, CAB was evaluated in patients with advanced prostate cancer (locally advanced affection or disseminated). In the subgroup analysis for patients with metastatic disease, a significant OR was seen for overall survival at 5 years for CAB (OR = 1.25; [95% CI: 1.05-1.48]) when compared with castration. However, when this analysis was limited to high quality studies, as identified by the review, the OR was not significant (OR = 1.34 [95% CI: 0.96-1.87]).222

RCT (1++)/RCT reviews In various reviews and in a study by Moinpour et al, CAB was found to be more toxic than castration: diarrhoea (9.7% vs 1.8%), gastrointestinal pain (74% vs 1.6%), ophthalmologic events (29% vs 5.4%), emotional disturbance at 3 and 6 months (p < 0.003) and haematological toxicity.223,225,226,229

8.1.2 Immediate vs delayed hormone therapy

Treatment with androgen suppression can be implemented immediately (when lymph node disease or metastasis is diagnosed) or deferred (when signs and symptoms of clinical development appear).4,217

The studies found show the results of patients with advanced prostate cancer without differentiating between locally advanced or disseminated affectionation.

RCT (1+) In the Jordan et al study, immediate and delayed hormone therapy were compared in patients with advanced prostate cancer. Subgroup
Analysis of the patients with metastasis showed an overall survival hazard ratio at one year of HR = 1.29 (95% CI: 0.83-2.02), at 5 years it was HR = 1.00 (95% CI: 0.65-1.55) and at 10 years it was HR = 1.88 (95% CI: 0.86-4.07).

The Loblaw publication, which contains the recommendations from the American Society of Clinical Oncology (ASCO) on this issue, presents evidence of moderately better results for cancer-specific mortality with the immediate use of androgen deprivation in patients with advanced prostate cancer, although there were no differences for overall mortality.

The review published by Nair et al. includes studies of patients with advanced prostate cancer treated with hormone therapy (as a single treatment or adjuvant with radical prostatectomy) prior to the widespread use of PSA as a diagnostic tool. No differences were found for cancer-specific survival when comparing the immediate and delayed treatments.

Two publications agree in concluding that delayed HT is more cost-effective than the immediate treatment in patients with advanced prostate cancer.

The following side effects were found to be more frequent in the immediate HT group than in the delayed HT group: genitourinary (48% vs 13%), hot flushes (59% vs 0%), gynecomastia (22% vs 2%) and incontinence (43% vs 30%). With regard to cardiovascular deaths, the results were similar for both groups.

It is considered important to assess the use of immediate HT vs delayed in a different way for symptomatic and asymptomatic patients.

Moreover, as cancer-specific survival tends to be greater in patients with immediate HT, the patient's life expectancy is an important factor when considering the type of hormonal treatment to apply.

### 8.1.3 Intermittent vs continuous hormone therapy

As with patients with prostate cancer in biochemical progression, the use of intermittent androgen suppression hormone therapy in men with disseminated prostate cancer is justified for various reasons, such as improving the quality of life in periods without hormone therapy, reduced costs and the possibility of delaying the appearance of androgen-independence in the prostate tumour.

Lane et al. found that in a number of patients with metastatic prostate cancer subjected to intermittent treatment, overall survival at 5 years was 70%.

The Leval et al. study included patients with advanced prostate cancer (locally advanced affection or disseminated) in biochemical progression after radical prostatectomy. They were subjected to intermittent vs continuous hormone therapy. The median progression rate at 3 years was 7% vs 38.9%. A cancer-specific mortality of 5.7% was found in those treated with intermittent HT.
(median follow-up: 2.4 years). No significant differences were found when comparing intermittent vs continuous HT for the risk of PSA relapse (defined as PSA ≥ 10 ng/ml). In patients with Gleason > 6, there was a trend towards lower risk of PSA relapse in the intermittent HT group (RR = 0.47 [95% CI: 0.04-4.96]; p = 0.53)

Most patients who received HT experienced mild-moderate adverse effects due to androgen suppression (hot flushes, loss of libido and erectile dysfunction), which almost always disappeared when the hormone treatment stopped.

Treatment was stopped because of severe gastrointestinal toxicity in 4.4% of patients who received continuous HT and 2.9% of the intermittent group.

**RCT (1+)**

With regard to sexual function, the Hering et al study obtained better results for the intermittent HT group when hormone treatment was stopped (those impotent at the end of treatment: 18/25 vs. 18/18; RR = 0.72; [95% CI: 0.56-0.92]; p = 0.008).

**Expert reviews (4)**

With regard to the economic impact of both these treatments, the clinical practice guideline from the United Kingdom National Institute for Health and Clinical Excellence (NICE) suggested that intermittent HT probably has a lower cost than the continuous despite the need for greater monitoring.

**Case series (3)**

As to how to administer this treatment, the Lane et al case series only considered the application of intermittent HT to patients who had received androgen deprivation for at least 9 months and had reached PSA < 4 ng/ml or a 90% reduction in the levels prior to treatment. If a patient who had stopped androgen deprivation reached a PSA > 20 ng/ml, another cycle of androgen deprivation was started.

The Hussain et al study compared intermittent with continuous hormone treatment, but without any conclusive results. It included patients with metastatic prostate cancer who had received androgen deprivation for at least 7 months and had reached PSA < 4 ng/ml (stable or declining during the sixth and seventh months). Intermittent or continuous treatment was chosen at random. Where deprivation was stopped, the initial pattern was repeated if the PSA of the patient began to rise or clinical symptoms of disease progression appeared. After this cycle of androgen deprivation, if the PSA returned to normal, HT was stopped. Patients were monitored every 6 months.

### 8.1.4 Second-line hormone therapy

In the therapeutic scheme followed in this guideline, first line hormone therapy is considered as castration (chemical or surgical) or complete androgen blockade. If castration starts to fail, an antiandrogen is added. If CAB becomes less effective, the antiandrogen is removed, which paradoxically has a beneficial effect (known as "antiandrogen withdrawal syndrome")

If there is biochemical or clinical progression after exhausting the first line hormone treatment possibilities, androgen-independence will be considered after checking testosterone is at castration levels.

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8 In some documents the failure of first-line hormone therapy is said to be "hormone refractory", a term that in this guideline indicates failure of any type of hormone therapy (first or second line).
In patients with androgen-independent prostate cancer (AIPC), treatment with cytotoxic chemotherapy (CT, such as docetaxel and oestramustine) or second-line hormone therapy: ketoconazole, progestins (such as MPA), oestrogens, corticosteroids, bicalutamide at high doses (150 mg/day) and other hormone manoeuvres can be suggested\(^{16,17}\).

Currently, first-line chemotherapy in patients with prostate cancer includes docetaxel (see section 8.2), although other treatment programmes have been used with drugs such as oestramustine, mitoxantrone, vinorelbine or etoposide\(^{237}\).

**RCT** In a study comparing medroxyprogesterone acetate (MPA) vs oestramustine in patients with AIPC, no differences were found for the progression at 3 months nor for overall survival at 1 year. However, differences were seen in the time to progression: 12 to 56 weeks in 13/51 patients with MPA, while 22 to 28 weeks in 4/51 patients with oestramustine (\(p = 0.05\)). The oestramustine treatment was discontinued in 8/51 patients due to side effects (nausea, vomiting and diarrhoea), and in 3/51 patients who received MPA (oedema, cardiovascular toxicity and increased pain)\(^{238}\).

**Expert review** The only clinical trial found that was aimed at comparing second-line HT v CT with docetaxel was the ECOG 1899\(^{239}\), which was stopped early due to inability to attract patients (17 between 2003 and 2005)\(^{240,241}\). According to a Ryan et al narrative review, this fact indicates that few of these patients agreed to be included in an experimental study that directly compared CT with docetaxel vs second line HT, as they considered it unlikely that there would be a sufficiently robust study to resolve this question in the future\(^{241}\).

**RCT** Some studies have assessed second line hormone therapy or chemotherapy with docetaxel in patients with AIPC, but the two treatments were not compared directly\(^{242-244}\).

**RCT** In the Small et al publication, two second-line HT programmes (ketoconazole 400 mg/day + hydrocortisone 40 mg/day + antiandrogen withdrawal vs antiandrogen withdrawal) were evaluated in patients with AIPC. Survival results obtained were 15.3 months vs 16.7 months (difference not statistically significant)\(^{242}\).

**RCT** Petrylak et al analysed 2 CT treatment programmes (docetaxel + oestramustine vs mitoxantrone + prednisone) that gave a statistically significant overall survival difference of 17.5 months vs 15.6 months\(^{243}\).

**RCT** The Tannock et al study compared other CT treatment programmes (docetaxel vs mitoxantrone + prednisone). Statistically significant survival results of 18.9 months vs 16.5 months were obtained\(^{244}\).

**Expert review** Among the reasons given for recommending CT as soon as the tumour becomes hormone-resistant are the following:

- It has been proven that early use of CT is effective in other solid tumours (breast, colorectum), where applying it immediately after surgery is considered the standard treatment when the disease is disseminated.
According to some authors, in earlier stages of the disease there may be a lower number of androgen-independent cells, which would mean CT would have a greater cumulative effect. For some it may be ethically unacceptable to delay offering a treatment that may prolong life and reduce pain.

Expert review (4)

As for arguments that, according to Ryan et al have been used to recommend the use of CT alone in patients with advanced and symptomatic disease are the following:

- In the TAX 327\textsuperscript{244} study, no significant differences were found in the mortality hazard ratio when comparing symptomatic and asymptomatic patients, which for some authors suggests that delaying CT treatment until there are clinical signs does not alter the results.
- The length of time to disease progression induced by androgen deprivation is important, even in patients with metastasis.
- Secondary hormone treatments, such as ketoconazole have some use.
- Some argue that, although it is possible that the response to second line hormone therapy is slightly less than with chemotherapy, when this response is managed in an individual (by measuring PSA), the final survival of the patient may be lengthened. Therefore, before offering CT, it may be appropriate to first of all try a second-line hormone treatment, particularly in patients with a higher disease burden without significant tumour pain.
- There are authors who believe that early use of chemotherapy may have significant adverse effects, and that for many patients it is not necessary as it does not provide significant benefits.
- As there is no standard second-line CT (currently the alternative may be mitoxantrone), some believe it is better to use only docetaxel when there is no alternative treatment. Failure to do so, according to these authors, means that resistance to this treatment may appear too soon, leaving the patient without further treatment alternatives for palliation once the tumour becomes symptomatic.

In conclusion, with the information available so far, it is difficult to know whether there are differences between the two treatment options in terms of safety or efficacy.

**Summary of evidence**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>CAB provides a 3% improvement in survival at 5 years when compared with castration\textsuperscript{222-227}. The benefit seems limited to patients who take non-steroidal antiandrogens\textsuperscript{223-226}.</td>
</tr>
<tr>
<td>1+</td>
<td>The overall mortality hazard ratio showed a small statistically significant difference in favour of the blockade with bicalutamide compared with castration (HR = 0.8)\textsuperscript{228}.</td>
</tr>
<tr>
<td>1++</td>
<td>When comparing CAB vs orchidectomy, better results were found in cancer-specific survival, except when using CAB with cyproterone acetate\textsuperscript{223,226}.</td>
</tr>
<tr>
<td>1++</td>
<td>In a subgroup analysis, patients with metastastic disease had a significant OR for overall survival at 5 years for CAB (OR = 1.25 [95% CI: 1.05-1.48]) when compared with castration. When the analysis was limited to high-quality studies, the OR was not significant (OR = 1.34 [95% CI: 0.96-1.87])\textsuperscript{225}.</td>
</tr>
<tr>
<td>++</td>
<td>CAB has more toxic effects than castration: diarrhoea (9.7% v 1.8%), gastrointestinal pain (74% v 1.6%), ophthalmologic events (29% v 5.4%), emotional disturbance at 3 and 6 months (p &lt; 0.003) and haematological toxicity\textsuperscript{223,225,226,229}.</td>
</tr>
<tr>
<td>+</td>
<td>In a subgroup analysis, the relative overall survival (for deferred HT vs immediate) in patients with metastatic prostate cancer at 1 year gave a survival hazard ratio, HR = 1.29, at 5 years HR = 1.00, at 10 years HR = 1.88 (none of the differences were statistically significant)\textsuperscript{230}.</td>
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<tr>
<td>+</td>
<td>For cancer-specific mortality, immediate HT had moderately better results in patients with \textit{advanced} prostate cancer (locally advanced or disseminated). For global mortality, there were no differences\textsuperscript{231}.</td>
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<tr>
<td>+</td>
<td>In patients with \textit{advanced} prostate cancer treated with immediate or delayed HT (such as single treatment or adjuvant to radical prostatectomy) before PSA was widely used as a diagnostic tool, no differences were found for cancer-specific survival\textsuperscript{217}.</td>
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<tr>
<td>++/+</td>
<td>Delayed HT is more cost-effective in patients with \textit{advanced} prostate cancer (locally advanced affection or disseminated)\textsuperscript{223,231}.</td>
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<tr>
<td>+</td>
<td>Side effects associated with the treatment were more often in the immediate HT group than the deferred HT group: genitourinary (48% vs 13%), hot flushes (59% vs 0%), gynecomastia (22% vs 2%), incontinence (43% vs 30%)\textsuperscript{232}. Cardiovascular deaths: similar results were found for the immediate and delayed treatment\textsuperscript{230,233}.</td>
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<tr>
<td>3</td>
<td>In patients with metastatic prostate cancer subjected to intermittent treatment, overall survival at 5 years was 70\textsuperscript{234}.</td>
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<td>-</td>
<td>In patients with \textit{advanced} prostate cancer (locally advanced affectation or disseminated), the median progression rate at 3 years was significantly less for intermittent HT compared with continuous HT (7% vs 38.9%)\textsuperscript{219}.</td>
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<tr>
<td>-</td>
<td>In patients with \textit{advanced} prostate cancer, after a median follow-up of 2.4 years, 5.7% of those treated with intermittent HT had died from the tumour\textsuperscript{219}.</td>
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<tr>
<td>-</td>
<td>In patients with \textit{advanced} prostate cancer, no significant differences were found when comparing intermittent HT vs continuous HT when analysing the risk of undergoing biochemical progression (defined as PSA \geq 10 ng/ml). For Gleason &gt; 6, there was a trend towards lower risk of biochemical progression in the intermittent HT group (RR = 0.47 [95% CI: 0.04-4.96]; p = 0.53)\textsuperscript{219}.</td>
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<tr>
<td>-</td>
<td>Most patients who received continuous or intermittent HT experienced mild-moderate adverse effects due to androgen suppression (hot flushes, loss of libido and erectile dysfunction), which in most cases disappeared when the hormone treatment was stopped\textsuperscript{219}.</td>
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<tr>
<td>-</td>
<td>Treatment was stopped because of severe gastrointestinal toxicity in 4.4% of patients treated with continuous HT and 2.9% of those receiving intermittent\textsuperscript{219}.</td>
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<tr>
<td>+</td>
<td>For impotence rates, better results were found for the intermittent HT group while the treatment was stopped (18/25 vs 18/18, RR = 0.72 [95% CI: 0.56-0.92]; p = 0.008)\textsuperscript{235}.</td>
</tr>
<tr>
<td>+</td>
<td>When comparing medroxyprogesterone acetate (MPA) vs oestramustine in patients with androgen-independent prostate cancer (AIPC), there were no differences for progression at 3 months nor for overall survival at 1 year. However, there were differences for time to progression: 12 to 56 weeks in 13/51 MPA patients, 22 to 28 weeks in 4/51 with oestramustine (p = 0.05)\textsuperscript{238}.</td>
</tr>
</tbody>
</table>
When comparing MPA vs oestramustine in patients with AIPC, the treatment was discontinued in 8/51 patients receiving oestramustine due to side effects (nausea, vomiting and diarrhoea) and in 3/51 patients receiving MPA (oedema, cardiovascular toxicity and increased pain)\(^2^{38}\).

The only study that has tried to compare second-line HT vs CT with docetaxel was the ECOG 1899\(^2^{39}\), which had to be stopped early due to low patient numbers (17 between 2003 and 2005)\(^2^{40,241}\). It is unlikely to find a sufficiently robust study to directly compare CT vs second-line HT in these patients\(^2^{41}\).

The treatment with second-line HT (ketoconazole + antiandrogen withdrawal vs antiandrogen withdrawal) in patients with AIPC, gave survival results of 15.3 months vs 16.7 months (difference not statistically significant)\(^2^{42}\).

Treatment with CT (docetaxel + oestramustine vs mitoxantrone + prednisone) in patients with AIPC had survival results of 17.5 months vs 15.6 months (a statistically significant difference)\(^2^{43}\).

Treatment with CT (docetaxel vs mitoxantrone + prednisone) in patients with androgen-independent prostate cancer (AIPC), had survival results of 18.9 months vs 16.5 months (a statistically significant difference)\(^2^{44}\).

Some authors have recommended applying CT as soon as the tumour becomes hormone resistant for the following reasons\(^2^{41}\):
- This strategy has proven effective in other solid tumours, where applying CT immediately after surgery is the standard treatment in disseminated disease.
- In the early stages there may be fewer androgen-independent cells, which would increase the cumulative effect of the CT.
- For some it may be ethically unacceptable to delay treatment which may prolong life and reduce pain.

Some authors have recommended using CT alone in patients with advanced and symptomatic disease for the following reasons\(^2^{41}\):
- In the TAX 327 study\(^2^{44}\), no significant differences were found in the mortality hazard ratio when comparing symptomatic and non-symptomatic patients, which some authors suggest means that delaying therapy until clinical signs appear does not alter the results.
- The time to disease progression induced by androgen deprivation is substantial, even in patients with metastasis.
- Secondary hormone treatment is of some use.
- Some argue that, although it is possible that the proportion of responses to second-line hormone therapy is slightly lower than with CT, where this response is achieved in an individual (by measuring the PSA), the possibilities of final survival in the patient may be higher. Therefore, before offering CT, it may be appropriate to firstly try a second-line hormone treatment, particularly in patients with a higher disease burden without significant tumour pain.
- As there is no standard second-line CT, some consider it better to be conservative with docetaxel and use it only when CT is really required. If not, they believe that resistance to this treatment may appear too soon, leaving the patient without further treatment alternatives for palliation once the tumour becomes symptomatic.
### Recommendations

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<table>
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<tbody>
<tr>
<td><strong>A</strong></td>
<td>In patients with disseminated prostate cancer for which hormone therapy is indicated, (surgical or chemical) castration is recommended as a first-line treatment.</td>
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<tr>
<td><strong>D</strong></td>
<td>In patients with symptomatic disseminated prostate cancer, hormone treatment is recommended.</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>In patients with asymptomatic disseminated prostate cancer spread, immediate or deferred hormone therapy can be offered, the latter when symptoms appear.</td>
</tr>
<tr>
<td></td>
<td>In patients with disseminated prostate cancer and low tumour burden, intermittent androgen suppression can be evaluated as an alternative to continuous androgen suppression if there is a good response to initial hormone treatment.</td>
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<tr>
<td></td>
<td>To be able to indicate intermittent hormone therapy, the patient must have received androgen deprivation for at least 7 months and reached a PSA &lt; 4 ng/ml (stable or in decline during the sixth and seventh months), or a 90% reduction from pre-treatment levels. Monitoring will be carried out every 6 months. Patients who have stopped androgen deprivation will receive another cycle on request, when the PSA increases or when clinical symptoms of disease progression appear. If the PSA returns to normal after the new round of androgen deprivation, hormone therapy can be stopped again.</td>
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<tr>
<td></td>
<td>Patients with disseminated androgen-independent prostate cancer (when both androgen suppression and complete androgen blockade have failed) can be offered second-line hormone therapy before starting chemotherapy treatment.</td>
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<td>RESEARCH RECOMMENDATION:</td>
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<tr>
<td></td>
<td>Patients with disseminated androgen-independent prostate cancer (when both androgen suppression and complete androgen blockade have failed) should be offered inclusion in clinical trials to evaluate the safety and efficacy of second-line hormone therapy, comparing it to chemotherapy which has proven effective.</td>
</tr>
</tbody>
</table>

#### 8.2 Chemotherapy

**Questions to answer:**

- In patients with androgen-independent disseminated prostate cancer, what is the safest and most effective treatment for improving overall survival, clinical or biochemical response, progression-free survival and reduction of side effects: oestramustine, mitoxantrone, docetaxel, docetaxel-oestramustine, vinorelbine or etoposide?

- In patients with androgen-independent prostate cancer who are going to receive chemotherapy, is it safer and more effective to start it at biochemical failure or wait for clinical progression?

- In patients with disseminated prostate cancer in progression after hormone treatment who are going to receive chemotherapy, does removing LHRH agonists modify the safety and efficacy?
8.2.1 Choosing first-line chemotherapy treatment

In men with hormone-refractory prostate cancer, other alternative therapies need to be evaluated. One possibility is systemic cytotoxic chemotherapy (CT), whose results vary depending on the drugs used. Both docetaxel and mitoxantrone associated with corticosteroids are administered as standard. Prednisone or dexamethasone can also be used\textsuperscript{237}.

The Shelley et al review\textsuperscript{237} examines the use of CT in patients with androgen-independent prostate cancer (AIPC). It has little in the way of studies comparing these drugs with each other.

\textit{Mitoxantrone + corticoid vs corticoid}

\textbf{RCT} The first chemotherapy considered as standard treatment in patients with AIPC was mitoxantrone, which was analysed by several studies comparing mitoxantrone (12-14 mg/m\textsuperscript{2} dose every 3 weeks) + corticoid vs corticoid\textsuperscript{245-247}.

\textbf{RCT} The use of mitoxantrone achieved a significant decrease in pain intensity (down 2 points on a scale of 6). The percentage of patients achieving pain relief was 29\% vs 12\% (p = 0.01)\textsuperscript{247}.

\textbf{RCT} Mitoxantrone treatment also managed to increase the quality of life in patients, due to the improvement of emotional status (p = 0.04), the decrease of family disruption (p = 0.02), less pain frequency (p = 0.06) and the existence of less intense pain (p = 0.03), although difficulties in sexual and urological function favoured those treated with hydrocortisone only\textsuperscript{245}.

\textbf{RCT} In another study, the quality of life scales were generally better in patients who received mitoxantrone and responded to the mitigation of pain\textsuperscript{247}.

\textbf{RCT} In asymptomatic patients with a median follow-up of 22 months, the use of mitoxantrone increased the number of patients who achieved a reduction of over 50\% in PSA levels (p = 0.007)\textsuperscript{246}.

\textbf{RCT} The use of chemotherapy gave a small, but statistically significant, increase in the time to progression of the disease (p = 0.02\textsuperscript{245}; p = 0.018\textsuperscript{246}).

\textbf{RCT} None of the three mitoxantrone studies showed a significant increase in overall survival\textsuperscript{245-247}.

\textbf{RCT} The major toxicities associated with mitoxantrone included grade 3-4 neutropenia (7\%), nausea and vomiting, alopecia (24\%) and cardiotoxicity (66\%)\textsuperscript{247}. In another study, grade 3-4 cardiotoxicity appeared in 5\% of patients who received mitoxantrone, and haematological toxicity was significantly higher in patients who received the chemotherapy\textsuperscript{245}.

\textit{Docetaxel + corticosterone vs mitoxantrone + corticosterone}

\textbf{RCT} The docetaxel efficacy results were compared with mitoxantrone (the chemotherapy reference at the time) in the 2004 Tannock et al study\textsuperscript{244}, which included 1,006 men with AIPC. There were two different docetaxel administration regimes: some patients received a dose of 75 mg/m\textsuperscript{2} every 3 weeks and others a weekly dose (30 mg/m\textsuperscript{2}/week over 6 weeks). The mitoxantrone was administered at doses of 12 mg/m\textsuperscript{2} every 3 weeks.
When docetaxel was compared with mitoxantrone, the mortality hazard ratios were: (HR = 0.76 [95% CI: 0.62-0.94]; p = 0.009) for docetaxel every 3 weeks and (HR = 0.91 [95% CI: 0.75-1.11]; p = 0.36) for the weekly scheme. This showed a significant improvement in overall survival with the 3 week docetaxel regime, compared with the mitoxantrone (24% reduction in the risk of death).

A significant reduction was also noted in pain in patients who received the 3-week docetaxel regime compared with mitoxantrone (35% vs 22%; p = 0.01) but not with the weekly programme (31 %). The median pain response duration (3.5 vs 5.6 months) was not significant different between the groups.

The quality of life also showed a significant improvement in patients treated with the 3-week docetaxel regime compared with those treated with mitoxantrone (22% vs 13%; p = 0.009).

Degree 3 and 4 neutropenia in patients included in the 3-week regime was statistically significantly more frequent than those who received weekly docetaxel or mitoxantrone (32% vs 2% vs 22%), although the frequency of febrile neutropenia was less than 4% in all groups.

There was a high incidence of nausea and vomiting in all programmes (38% to 42%). Diarrhoea was significantly more frequent in the docetaxel regimes.

Interruption of treatment with docetaxel was due to fatigue, musculoskeletal events, changes in the nails, sensory neuropathy and infection. In the mitoxantrone group, the main reason was due to cardiac dysfunction.

**Docetaxel + oestramustine + corticosteroid vs mitoxantrone + corticosteroid**

RCT (1++) The combination of docetaxel and oestramustine has also been compared with mitoxantrone in patients with AIPC. The Petrylak et al study\textsuperscript{243} administered docetaxel to one group (60 mg/m\textsuperscript{2} on day 2) then oestramustine (280 mg/m\textsuperscript{2} days 1-5) and mitoxantrone (12 mg/m\textsuperscript{2} on day 1) to another group. In the Oudard et al study\textsuperscript{248}, there were 3 branches of treatment: one that received docetaxel at a dose of 70 mg/m\textsuperscript{2} (administered on day 2 every 3 weeks) and oestramustine (280 mg/m\textsuperscript{2} administered 3 times a day on days 1-5); another that received docetaxel at a dose of 35 mg/m\textsuperscript{2} (days 2 and 9, repeated over a 3 week cycle) and oestramustine (as above), and another that received mitoxantrone (12 mg/m\textsuperscript{2} every 3 weeks).

RCT (1++) In the Petrylak et al study there was a significant improvement in overall survival for those treated with docetaxel and oestramustine (17.5 months vs 15.6 months; p = 0.02)\textsuperscript{243}. However, in the Oudard et al study, although the median overall survival was greater for those treated with docetaxel (18.6 and 18.4 months) than for mitoxantrone (13.4 months), there were no significant differences between the regimes (p = 0.3)\textsuperscript{248}.

RCT (1++) Regarding disease progression, significant improvements were found for those receiving combination treatment [6.3 months v 3.2; p <0.001 in one study\textsuperscript{243}; p <0.00001 in the other\textsuperscript{248}].
The percentage of patients who achieved a PSA response (at least a 50% reduction in levels) was statistically significantly better in patients treated with docetaxel and oestramustine [50% vs 27%; p <0.001 in one study; p <0.00001 in the other).

With regard to pain relief, the Petrylak et al study found no significant differences between the two groups when evaluated by patients. However, the Oudard et al showed a statistically significant improvement in pain index for each of the two docetaxel groups (70 mg/m² and 35 mg/m²) when compared with mitoxantrone (40% and 29% vs 17%).

There was a significant improvement in the ECOG performance status of patients treated with docetaxel compared with mitoxantrone (60% and 48% vs 28%, respectively).

With the docetaxel-oestramustine combination, there were more gastrointestinal side effects (p = 0.001), nausea and vomiting (p = 0.001), infection (p = 0.004), metabolic toxicity (p <0.001) and neurological dysfunction (p = 0.001). In addition, there was oestramustine-induced thrombosis in 7% of the patients treated with docetaxel, despite receiving anticoagulant treatment.

Granulocytopenia grade 3 and 4 was the most common toxicity in patients treated with docetaxel 70 mg/m² and mitoxantrone (37% and 48% respectively), but this was not seen with the lower dosage of docetaxel.

**Docetaxel + oestramustine + corticosteroid vs docetaxel + corticosteroid**

Comparison of docetaxel-oestramustine v docetaxel in patients with androgen-independent prostate cancer (AIPC) and metastatic prostate cancer was evaluated by the Eynard et al study, which applied docetaxel (70 mg/m² on day 2) and oestramustine (280 mg/m² administered twice daily on days 1-5) in a group of patients (n = 47) and docetaxel (75 mg/m² on day 1) in the other (n = 44).

There was a statistically significant difference in the PSA response (decrease in PSA level in ≥50% maintained for ≥3 weeks), which was: 68% [95% CI: 55-81] v 30% [95% CI: 16-43]. The median PSA response duration was 6.0 months in both groups.

The median time to progression was 5.7 months [95% CI: 4.7-6.8] vs 2.9 months [95% CI: 2.0-6.9], and the median survival time was 19.3 months [95% CI: 14.6-25.9] vs 17.8 months [95% CI: 11.8-20.9], both without significant differences.

Haematological and non-haematological toxicity plus the quality of life were similar in both groups.

6% of patients treated with the combination had phlebitis, possibly due to the oestramustine. One patient in each group decided to discontinue the study because of toxicity. One treatment-related death (pulmonary oedema) occurred before 30 days in the docetaxel group.
Although the efficacy results seem similar, it must be remembered that, in the Petrylak et al study, 15% of the cardiovascular events appeared in the docetaxel-oestramustine group. Because the patients were elderly and had associated comorbidities, it was necessary to assess the need to add oestramustine to the docetaxel treatment. This was because it only provides an increase in the rate of PSA response at the expense of a possible increase in toxicity.

8.2.2 Chemotherapy start time

An increase in PSA levels is a signal that prostate cancer is in progression, and it also helps to evaluate response to treatment. In patients with androgen-independent prostate cancer (AIPC) for whom it has been decided to administer cytotoxic chemotherapy (CT), this can be started at biochemical recurrence or clinical progression.

No studies have been found that directly compare the use of CT in these two situations, since the effectiveness of chemotherapy has only been assessed at clinical progression.

Expert review

The European Association of Urology clinical practice guideline recommends establishing a chemotherapy regime for AIPC patients who have two consecutive PSA increases above the reference values, and a PSA level above 5 ng/ml. It also recommends the decision for the start of the chemotherapy treatment should be done on an individual basis.

8.2.3 Using LHRH agonists with CT

In AIPC patients treated with frontline hormone therapy (androgen suppression or complete androgen blockade) for whom it is decided to apply cytotoxic CT, there is the possibility of maintaining the treatment with LHRH agonists or not.

No studies directly comparing these two treatment options have been found, not even in the Cochrane review for Shelley et al 2006, which analyses the use of CT in patients with AIPC.

Two recent non-systematic reviews (2006 and 2007) include a brief comment stating that chemical castration treatment can be continued, but no controlled studies to support this assertion are shown.

The usual strategy for handling these patients is to maintain treatment with LHRH agonists when initiating CT treatment. This is usually justified by health professionals on the grounds that it prevents stimulation of any hormone-sensitive cells the patient may have.

It should be remembered that, when a patient has received treatment with LHRH agonists for a long time and they are removed, testosterone levels may take more than a year to regain their normal values.
**Summary of evidence**

<table>
<thead>
<tr>
<th>1+</th>
<th>A significant reduction in pain intensity with the use of mitoxantrone when compared with corticosteroid was achieved. The percentage of patients achieving palliation was 29% vs 12% (p = 0.01)(^2)(^4)(^7).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>An increase in the quality of life was achieved with mitoxantrone + corticosteroid due to an improvement in emotional state (p = 0.04), reduction of family disruption (p = 0.02), less frequent pain (p = 0.06) and less intense pain (p = 0.03). Difficulties in sexual and urological function favoured the hydrocortisone-only option(^2)(^4)^. The quality of life scales were generally better in patients who received mitoxantrone and they responded to pain mitigation(^2)(^4)(^7).</td>
</tr>
<tr>
<td>1+</td>
<td>In asymptomatic patients with a median follow up of 22 months, the use of corticosteroid and mitoxantrone increased the number achieving a reduction of more than 50% in PSA levels (p = 0.007), compared with those receiving only corticosteroid(^2)(^4)(^6).</td>
</tr>
<tr>
<td>1+</td>
<td>Using mitoxantrone with corticosteroid, a small, but statistically significant, increase was found was in the time to disease progression (p = 0.02; p = 0.018), compared with only corticosteroid(^2)(^4)(^5),(^2)(^4)(^6).</td>
</tr>
<tr>
<td>1+</td>
<td>Mitoxantrone with corticosteroid, compared with corticosteroid, failed to significantly decrease overall survival(^2)(^4)(^5)-(^2)(^4)(^7).</td>
</tr>
<tr>
<td>1+</td>
<td>Toxicities associated with mitoxantrone include: neutropenia grade 3-4 (7%), nausea and vomiting, alopecia (24%) and cardiotoxicity (66%)(^2)(^4)(^7). Grade 3-4 cardiotoxicity appeared in 5% of patients who received mitoxantrone. Haematological toxicity was significantly higher for the mitoxantrone group(^2)(^4)(^5).</td>
</tr>
<tr>
<td>1++</td>
<td>When docetaxel was compared with mitoxantrone, the mortality hazard ratio was (HR = 0.76; [95% CI: 0.62-0.94]; p = 0.009) for docetaxel every 3 weeks and HR = 0.91; [95% CI: 0.75-1.11]; p = 0.36) for the weekly regime. There was a significant improvement in overall survival with the 3-week docetaxel regime compared with mitoxantrone (24% reduction in the risk of death)(^2)(^4)(^4).</td>
</tr>
<tr>
<td>1++</td>
<td>There was a significant pain reduction for patients who received the 3-week docetaxel regime compared with mitoxantrone (35% vs 22%; p = 0.01) but not with the weekly regime (31%). The median pain response duration (3.5 months vs 5.6 months) was not significantly different between the two groups(^2)(^4)(^4).</td>
</tr>
<tr>
<td>1++</td>
<td>The quality of life showed significant improvement in patients treated with 3-week docetaxel regime compared with mitoxantrone (22% vs 13%; p = 0.009)(^2)(^4)(^4).</td>
</tr>
<tr>
<td>1++</td>
<td>Grade 3-4 neutropenia was significantly more frequent in patients who received the 3-week regime than in those who received docetaxel weekly or mitoxantrone (32% vs 2% vs 22%), although the frequency of febrile neutropenia was less than 4% in all groups(^2)(^4)(^4).</td>
</tr>
<tr>
<td>1++</td>
<td>A high frequency of nausea and vomiting was recorded in all docetaxel and mitoxantrone treatment programmes (38% to 42%). Diarrhoea was significantly more frequent with docetaxel(^2)(^4)(^4).</td>
</tr>
<tr>
<td>1++</td>
<td>Interruption of treatment with docetaxel was due to fatigue, musculoskeletal events, changes in the nails, sensory neuropathy or infection. In the mitoxantrone group, the main reason was cardiac dysfunction(^2)(^4)(^4).</td>
</tr>
<tr>
<td>1++</td>
<td>One study found a significant improvement in overall survival for patients treated with docetaxel-oestramustine (17.5 months vs 15.6 months; p = 0.02), compared with</td>
</tr>
</tbody>
</table>
Regarding the time of disease progression, significant improvements were found for patients receiving the docetaxel-oestramustine treatment compared with patients treated with mitoxantrone [6.3 months vs 3.2 months; p < 0.001 in one study; p <0.00001 in another].

The percentage of patients who achieved a PSA response (decrease in PSA levels ≥ 50%) was significantly better in patients treated with docetaxel-oestramustine than in patients treated with mitoxantrone [50% vs 27%; p < 0.001 in one study; p <0.00001 in another].

With regard to pain relief, one study found no significant differences between docetaxel + oestramustine v mitoxantrone when evaluated. However, in another, a significant improvement was found in the pain index for each of the two docetaxel groups (70 mg/m² and 35 mg/m²) when compared with the mitoxantrone group (40% and 29% vs 17%).

There was a significant improvement in the ECOG performance status for patients treated with docetaxel (60% and 48% vs 28%, respectively), when compared with mitoxantrone.

Docetaxel-oestramustine was significantly more toxic (than mitoxantrone) with regard to gastrointestinal side effects (p = 0.001), nausea and vomiting (p = 0.001), infection (p = 0.004), metabolic toxicity (p < 0.001) and neurological dysfunction (p = 0.001). Oestramustine-provoked thrombosis was noted in 7% of patients treated with docetaxel despite receiving anticoagulant treatment.

Granulocytopenia grade 3 and 4 toxicity was more common in patients treated with docetaxel 70 mg/m² and mitoxantrone (37% and 48%, respectively), although this was not seen with the lower dose of docetaxel.

When comparing docetaxel-oestramustine v docetaxel, the PSA response (≥ 50% decrease in PSA level maintained for ≥ 3 weeks) was 68% [95% CI: 55-81] vs 30% [95% CI: 16-43], which was statistically significant. The median PSA response time was 6.0 months in both groups.

When comparing docetaxel-oestramustine v docetaxel, the median time to progression was 5.7 months [95% CI: 4.7-6.8] vs 2.9 months [95% CI: 2.0-6.9], with the median survival time of 19.3 months [95% CI: 14.6-25.9] vs 17.8 months [95% CI: 11.8-20.9], both without significant differences.

When comparing docetaxel-oestramustine v docetaxel, haematological and non-haematological toxicity, as well as the quality of life were similar in both groups.

When comparing docetaxel-oestramustine vs docetaxel, 6% of the patients treated with the combined form had phlebitis, possibly due to oestramustine. One patient in each group decided to leave the study due to toxicity. One death occurred before 30 days in the docetaxel-treated group (due to pulmonary oedema).

The European Association of Urology clinical practice guideline recommends establishing a chemotherapy regime for patients with AIPC who have two consecutive PSA increases above the reference values, and a PSA level above 5 ng/ml. It also recommends that the time to start chemotherapy should be decided on an individual basis.
No studies of a sufficient quality have been found which compare chemotherapy (CT) with CT + LHRH agonists\textsuperscript{237}.

Some authors believe that LHRH agonists may continue to be applied during chemotherapy treatment\textsuperscript{250,251}.

### Recommendations

| B | In patients with androgen-independent prostate cancer (AIPC) and metastasis, when chemotherapy treatment is proposed, it is recommended to use docetaxel (a 75 mg/m\textsuperscript{2} dose every 3 weeks) with corticosteroid. |
| √ | In patients with AIPC and metastasis, systematic association of docetaxel-oestramustine is not recommended. |
| √ | In patients with biochemical relapse, who are androgen-independent, asymptomatic and without documented metastasis disease, early chemotherapy treatment may be offered, especially within the framework of randomised trials. |
| RESEARCH RECOMMENDATION: | Patients with PSA relapse, who are androgen-independent, asymptomatic and without documented metastasis disease, should be offered inclusion in clinical trials comparing early chemotherapy treatment with delayed chemotherapy. |
| √ | In patients with androgen-independence for whom chemotherapy has been decided, LHRH agonists can continue to be applied. |
| RESEARCH RECOMMENDATION: | Patients with androgen-independent disseminated prostate cancer, for whom chemotherapy treatment has been decided, should be offered inclusion in clinical trials comparing the safety and efficacy of chemotherapy alone compared to chemotherapy associated with LHRH agonists. |

### 8.3 Bisphosphonates and radiopharmaceuticals

#### Questions to answer:

- In patients with disseminated prostate cancer, does intervention with bisphosphonates (zoledronic acid) compared with doing nothing improve event-free survival for bone pain and quality of life, and does it allow a reduction in the dose of painkillers?

- In patients with disseminated prostate cancer, does administering radiopharmaceuticals provide better control and/or a reduction of metastatic bone pain?
8.3.1 Bisphosphonates

Bone metastases appear in over 80% of patients with advanced prostate cancer: in the spine, pelvis, ribs and other locations. The median survival after its occurrence is approximately 3 years and, during this period, patients may suffer pain, hypercalcaemia, fractures and medullary compression. Bilateral of bone metastases are associated with the occurrence of pain and skeletal events. In prostate cancer, they are predominantly osteoblastic (bone-forming). It seems that before there is abnormal bone formation, osteoclastic resorption activation (bone destruction) appears, which is associated with bone pain. Bisphosphonates act by inhibiting bone resorption.

**Bone density and skeletal events**

**RCT (1+)** There is consistent evidence from randomised trials that treatment with bisphosphonates increases bone density in the spinal column in men receiving hormone therapy for prostate cancer. In patients treated with bisphosphonates, an average increase in bone density of 1-5% was seen in the first year of hormone treatment. However, a significant reduction of 0.4 - 4.9% was seen in those who received placebo or the standard treatment during the same period. The bisphosphonate group was about 5% greater.

**RCT (1++)** In patients with androgen-independent prostate cancer (AIPC), when compared with placebo, bisphosphonates achieved a modest reduction in skeletal events (such as the occurrence of pathological fractures, spinal compression, or the need for surgery or radiotherapy treatment for bone metastases): 37.8% vs 43.0%; absolute risk reduction of 5.2%.

**RCT (1-)** Saad et al studied the use of zoledronic acid in patients with AIPC, with a high loss rate (ranging between 62% and 72% depending on the treatment group). Zoledronate at a 4 mg dose caused a statistically significant decrease in the proportion of patients with skeletal events when compared with placebo. However, the difference with zoledronic acid at a dose of 8 mg (subsequently reduced to 4 mg) vs placebo was not significant. In addition, zoledronate reduced the incidence of skeletal events by 36% (RR = 0.640; p = 0.002). This decrease was highest in patients without pain. The bisphosphonate delayed the first skeletal episode by more than 5 months (p = 0.009, which was a significant difference when compared with placebo). A significant RR was seen for the proportion of patients with a skeletal event (RR = 0.71 [95% CI: 0.50-0.99]) when zoledronic acid was compared with placebo.

**RCT (1+/1-)** When comparing zoledronic acid with placebo or the standard treatment in patients with AIPC, symptomatic fractures did not appear in the year following the start of hormone therapy. As for asymptomatic fractures, there were no differences in the rates for both groups. In another study with the same design, the relative risk for the proportion of patients with pathological fractures was significant: RR = 0.57; [95% CI: 0.38-0.88].

**RCT (1+/1+)** In patients with AIPC, the rates of spinal compression, bone surgery and bone radiotherapy did not differ significantly when comparing bisphosphonate and placebo.
**Pain relief**

RCT  (1++) In men with AIPC, there was a non-significant trend towards better results with bisphosphonates when compared with placebo for pain relief in bone metastasis\(^2^{52}\).

RCT  (1-) The use of zoledronic acid at a dose of 8 mg in AIPC produces an improvement in the average pain rating at 15 months of treatment when compared with placebo (p = 0.026), but there were no significant differences when comparing bisphosphonate at a dose of 4 mg to placebo (p = 0.134). There were no significant differences in analgesia levels when comparing each of the bisphosphonate treatments with placebo\(^2^{59}\).

RCT  (1-) In men with AIPC, zoledronic acid produced significant reductions in bone pain in the long term, when compared with placebo\(^2^{60}\).

RCT  (1++) The use of bisphosphonates in patients with androgen-independent prostate cancer resulted in a decrease in consumption of painkillers when compared with placebo\(^2^{52}\).

**Survival**

RCT  (1-) In patients with AIPC, the median survival time was 464 days for patients treated with placebo, 546 days for patients who received zoledronate at 4 mg (p = 0.091), and 407 days for patients who received a dose of 8 mg (p = 0.386)\(^2^{59}\).

**Side effects and quality of life**

RCT  (1+) In men with metastatic prostate cancer treated with androgen deprivation, no significant differences were found in the rate of severe adverse effects when comparing bisphosphonates with placebo\(^2^{55,257,258}\).

RCT  (1-) In patients with AIPC, zoledronic acid resulted in a deterioration of kidney function: 15.2% of patients treated at a dose of 4 mg and 20.7% of those who received a dose of 8 mg, with 11.5% of those treated with placebo\(^2^{59}\).

RCT  (1++) In patients with AIPC, the quality of life did not differ significantly when comparing bisphosphonates and placebo\(^2^{52}\).

RCT  (1++) A systematic review in 2007\(^2^{63}\) found only 26 cases of mandibular osteonecrosis in patients treated with bisphosphonates, which had been previously reported. Of the 26 cases found, 87% occurred in women, 78% older than 60 years. For 80%, in the area of osteonecrosis, dental damage already existed or the patients had received treatment prior to surgery. There was no clear link found between the duration of treatment with bisphosphonates and the appearance of mandibular osteonecrosis. It should be remembered that the frequency of this adverse effect is very low: only 1 case appeared in a series of more than 7,000 women treated for 3 years with zoledronic acid. The estimated incidence is 1 case per 10,000-100,000 inhabitants/year in patients treated with bisphosphonates.

Despite this very low frequency, there is a Spanish Medicines Agency warning of mandibular osteonecrosis associated with bisphosphonates. It recommends a dental check-up...
before treatment and that the patient is not subjected to invasive dental interventions while undergoing intravenous treatment with bisphosphonates\textsuperscript{264}.

8.3.2 Radiopharmaceuticals

The majority of patients with androgen-independent prostate cancer (AIPC) have painful bone metastasis. Strontium-89 (Sr-89) and Samarium-153 (Sm-153) are beta-emitting radioisotopes administered intravenously for these patients\textsuperscript{4,16,265}.

\textit{Pain relief}

\textbf{RCT (1++)} When comparing the reduction of pain reported in patients treated with Sr-89 v placebo, no significant differences between the two treatments were found in the long term (1-3 years), but there were differences in the short term (5 weeks)\textsuperscript{266,267}. When Sr-89 was compared with local external beam radiotherapy (ERT), some studies found less pain in the group treated with Sr-89 + radiotherapy (RT), although in others there were no differences\textsuperscript{268,269}. When Sr-89 + local RT was compared with local RT, the reported pain was similar in both groups, but the appearance of new painful locations was significantly higher in the group receiving external radiotherapy\textsuperscript{270,271}.

It seems that the Sr-89 is effective for pain control in bone metastasis in up to 70\% of patients\textsuperscript{17}.

\textbf{RCT (1++)} The Sartor \textit{et al} study\textsuperscript{272} noted that the use of Sm-153 has positive effects on pain for 1-4 weeks after starting treatment, when compared with placebo (correlation coefficient $r = 0.78$; $p < 0.0001$). In addition, it decreased the use of opioids 3-4 weeks after starting the treatment ($p < 0.0284$).

When compared with placebo, Sm-153 achieved pain reduction in a greater proportion of patients after starting the treatment (38\% vs 18\%; $p = 0.008$). The same occurred 4 weeks after starting treatment (55\% vs 35\%)\textsuperscript{272}.

\textit{Survival}

\textbf{RCT (1++)} When comparing Sr-89 with local ERT, biochemical progression-free survival was comparable between the two groups, while overall survival was significantly greater in the group receiving ERT\textsuperscript{270}. However, when the same comparison was performed in a different trial, overall survival was similar in both groups\textsuperscript{271}.

\textbf{RCT (1++)} When comparing Sr-89 with placebo, the group treated with Sr-89 had a better overall survival at 2 years\textsuperscript{267}. When Sr-89 + local RT was compared with local RT, no differences in global survival were found\textsuperscript{268}. However, when Sr-89 + chemotherapy (CT) was compared with CT, better results for overall survival were found in the Sr-89 group\textsuperscript{273}.
Side effects and quality of life

RCT (1++) Sr-89 was associated with haematological toxicity (thrombocytopenia, neutropenia) in approximately 30-50% of patients who received it (usually moderate, grade ≤ 2)\textsuperscript{17}.

In randomised clinical trials that compared Sr-89 v local RT, the rate of adverse effects (haematological toxicity, nausea and vomiting) was similar in both groups\textsuperscript{270,271}.

Various study types (1++/4) The only statistically significant side effect associated with Sm-153 in a trial was temporary and slight myelosuppression\textsuperscript{272}. The European Association of Urology clinical practice guideline found that early use of radioisotopes may make it harder for the administration of chemotherapy, because they cause myelosuppression\textsuperscript{4}.

RCT (1++) When comparing Sr-89 + local RT v local RT, no significant differences were found regarding the quality of life\textsuperscript{269}.

In Spain, the use of Sr-89 for bone metastasis is only authorised for prostate cancer. Sm-153 is approved for this and other neoplasias affecting bone, such as in the breast or lung. Therefore, in Spain, the Nuclear Medicine Services usually have more experience in the use of samarium than strontium.

Although both Sr-89 and Sm-153 are beta-emitters\textsuperscript{265}, Sm-153 also emits gamma radiation. This means that the distribution of this radiopharmaceutical can be checked directly with an image test after the treatment, which cannot be done with strontium.

It seems that, in well-selected patients (when other analgesic treatments have failed), treatment with radiopharmaceuticals is effective in reducing pain. However, before proposing its use, first-line chemotherapy should be suggested first.

Summary of evidence

<table>
<thead>
<tr>
<th></th>
<th>In patients with metastatic prostate cancer treated with androgen deprivation, bisphosphonates were compared with placebo or the standard treatment. Those treated with bisphosphonates showed an average increase in bone density in the spinal column of 1-5% in the first year of hormone treatment. Those who received placebo or standard treatment showed a significant average decline of 0.4 – 4.9% during the same period. The difference between the two groups was about 5% for the bisphosphonates\textsuperscript{254-258}.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>In patients with androgen-independent prostate cancer (AIPC), there was a modest reduction of skeletal events in those treated with bisphosphonates v placebo: 37.8% vs 43.0%; an absolute risk reduction of 5.2%\textsuperscript{252}.</td>
</tr>
<tr>
<td>1++</td>
<td>In patients with AIPC, zoledronic acid at a dose of 4 mg produced a statistically significant decline in the proportion of patients with skeletal events when compared with placebo. However, when an 8 mg dose of zoledronic acid (subsequently reduced to 4 mg) was compared with placebo, the difference was not significant\textsuperscript{259}.</td>
</tr>
<tr>
<td>1-</td>
<td>In patients with AIPC, zoledronic acid reduced the incidence of skeletal events by 36% (RR = 0.640; p = 0.002)\textsuperscript{260}. This decrease was highest in patients without</td>
</tr>
<tr>
<td>Level</td>
<td>Evidence Description</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------</td>
</tr>
<tr>
<td>1-</td>
<td>Pain relief was improved with zoledronic acid at a dose of 8 mg after 15 months, compared to placebo (p = 0.026). No significant differences were found for a 4 mg dose compared to placebo (p = 0.134). There were no significant differences in analgesia levels comparing each of these doses with placebo.</td>
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</tr>
<tr>
<td>1++</td>
<td>The quality of life did not differ significantly when comparing bisphosphonate and placebo.</td>
</tr>
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<td>In patients with AIPC, the RR for the proportion of patients with a skeletal episode was significant (compared with placebo): RR = 0.71 [95% CI: 0.50 – 0.99].</td>
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</tr>
<tr>
<td>1-</td>
<td>In a study of patients with metastatic prostate cancer treated with androgen deprivation in which zoledronic acid was compared with placebo or the standard treatment, no symptomatic fractures occurred in the year following the start of hormone therapy. No differences in the rates of asymptomatic fractures in either groups was observed. In another test with the same design, the RR for the proportion of patients with pathological fractures was significant: RR = 0.57 [95% CI: 0.38 – 0.88].</td>
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<tr>
<td>1++</td>
<td>In patients with AIPC, the rates of spinal compression, bone surgery and radiotherapy did not differ significantly when comparing bisphosphonates with placebo.</td>
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<td>1++</td>
<td>In patients with AIPC, there was a trend towards better results for bone metastasis pain relief with bisphosphonates than with placebo.</td>
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<td>In patients with AIPC treated with zoledronate, the RR for the proportion of patients with a skeletal episode was significant (compared with placebo): RR = 0.71 [95% CI: 0.50 – 0.99].</td>
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<td>1-</td>
<td>Pain relief was improved with zoledronic acid at a dose of 8 mg after 15 months of treatment when compared with placebo (p = 0.026). However, no significant differences were found when comparing a 4 mg dose of bisphosphonate with placebo (p = 0.134). There were no significant differences in analgesia levels when comparing each of these doses with placebo.</td>
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<tr>
<td>1-</td>
<td>In patients with AIPC, zoledronic acid produced significant reductions in long term bone pain when compared with placebo.</td>
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<td>1++</td>
<td>In patients with AIPC, the quality of life did not differ significantly when comparing bisphosphonate and placebo.</td>
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A systematic review in 2007 found only 26 cases of mandibular osteonecrosis in patients treated with bisphosphonates, which had been previously reported. Of the 26 cases found, 87% occurred in women, 78% occurred in those older than 60 years and 80% in patients who had been subject to surgery or dental damage in the area of osteonecrosis prior to treatment. There was no clear link found between the duration of treatment with bisphosphonates and the appearance of mandibular osteonecrosis. It should be remembered that the frequency of this adverse effect is very low: only 1 case appeared in a series of more than 7,000 women treated for 3 years with zoledronic acid. The estimated incidence is 1 case per 10,000-100,000 inhabitants/year in patients treated with bisphosphonates.
When comparing the reduction of pain reported in patients treated with Sr-89 vs placebo, no significant differences between the two treatments were found in the long term (1-3 years), but there were differences in the short term (5 weeks). When Sr-89 was compared with local external beam radiotherapy (RT), some studies found less pain in the group treated with Sr-89 + radiotherapy (RT), although in others there were no differences. When Sr-89 + local RT was compared with local RT, the reported pain was similar in both groups, but the appearance of new painful locations was significantly higher in the group receiving external radiotherapy.

Sr-89 is effective for pain control in bone metastases in up to 70% of patients.

The use of Sm-153 has positive effects on pain 1-4 weeks after starting treatment, when compared with placebo (correlation coefficient r = 0.78; p < 0.0001). In addition, it decreased the use of opioids 3-4 weeks after starting treatment, when compared with placebo (p < 0.0284).

The use of Sm-153 manages to reduce pain at the start of the treatment in a greater proportion of patients (38% vs 18%; p = 0.008) when compared with placebo. The same occurred 4 weeks after starting treatment (55% vs 35%).

When comparing Sr-89 vs local ERT, biochemical progression-free survival was comparable between the two groups, while overall survival was significantly higher in the group receiving ERT. However, in a different test carrying out the same comparison, overall survival was similar in both groups.

When comparing Sr-89 with placebo, the group treated with Sr-89 showed better overall survival at 2 years. When Sr-89 + local RT was compared with local RT, there was no difference in global survival, but when comparing Sr-89 + chemotherapy (CT) with CT, overall survival in the Sr-89 group was better.

Sr-89 was associated with haematological toxicity (thrombocytopenia, neutropenia) in approximately 30-50% of patients who received it (usually to a moderate degree). In randomised trials comparing Sr-89 with local RT, the rate of adverse effects (haematological toxicity and nausea or vomiting) was similar in both groups.

The only statistically significant side effect associated with Sm-153 was temporary and slight myelosuppression. Early use of radioisotopes may make the administration of chemotherapy difficult, due to myelosuppression.

When comparing Sr-89 + local RT with local RT, no significant differences were found between the two groups regarding the quality of life.

**Recommendations**

**B** Routine use of bisphosphonates (zoledronic acid) as a preventive treatment for bone complications is not recommended. Zoledronic acid (4 mg every 3 weeks) can be offered in selected patients, and those who are hormone-independent or with demonstrated metastasis.

**A** Treatment with Sr-89 or Sm-153 can be proposed in men with androgen-independent prostate cancer (AIPC) when third level analgesics are required to adequately control bone pain. A correct haematological formula (> 3,500 leukocytes and > 150,000 platelets) and a bone scan showing bone metastasis are essential before administration.