Management of Advanced Prostate Cancer

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ABSTRACT

Most cases of advanced carcinoma of the prostate are hormonosensitive. The use of combined androgen blockade (CAB) seems to improve survival and quality of life, but only when combined with chemical castration by luteinizing-hormone-releasing hormone analog and without the use of steroidal antiandrogens. After CAB, further hormonal treatments remain efficacious, such as antiandrogen withdrawal followed by estrogens, aromatase inhibitors, and hormone-refractory prostate cancer multiple cytotoxic agents. For painful bone lesions, external beam radiotherapy, biphosphonates, and strontium 89 or samarium 153 provide pain relief. The use of new methods for the evaluation of response and quality of life will allow the rapid identification of effective treatments and permit powered phase III trials.

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INTRODUCTION

Prostate cancer is the cause of more than 1% of all deaths in men. Its incidence is increasing by 2%-3% per year. There are two main reasons for this increase. The first is increased life expectancy, and the second is that prostate-specific antigen (PSA) testing has enabled earlier and more accurate diagnosis of the disease. The general prognosis for diagnosed prostate cancer remains poor, with 70% survival at 10 years compared to the general population. About 50% of cases are diagnosed at a locally advanced stage, and about 30% have bone metastases at the time of diagnosis [1].

In 1996 in the United States, 317,000 new cases were diagnosed and 41,000 deaths reported. This latter figure represents 13% of all U.S. cancer deaths. In lay terms, this means that one death from prostate cancer occurred every 13 minutes [2]. In 1990, similar figures were recorded in France, with 17,600 new cases and 9,200 deaths reported (11% of all cancer deaths) [3]. However, in 1999 the 33rd annual compilation of cancer statistics [4] showed that the incidence of prostate cancer had decreased significantly with a decline in death rate of 11% since 1991. These statistics also reported an increase of 20% in 10-year survival between 1988 and 1995.

Systemic treatments for prostate cancer include various types of hormone therapy. Biphosphonates or radionuclides such as strontium 89 or other isotopes may be used in cases where bone lesions are identified. Other treatments include external radiotherapy and surgery. Chemotherapy has become an additional option when hormone treatment fails [5, 6].

TREATMENT OPTIONS FOR HORMONE-SENSITIVE DISEASE

Around 75% of metastatic prostate cancers are hormone sensitive. The average time for response to androgen deprivation is about 18 months; survival after second-line treatment varies from 6 to 10 months [7].

Early Treatment

For symptomatic patients or for those with progressive disease, hormonal treatment is considered compulsory. However, for nonsymptomatic hormone-sensitive patients this may not necessarily be the case. Hormonal treatment has unwanted side effects, particularly of a sexual nature. The costs of such treatment may also be considerable. It is also important to remember that hormone treatment continues to remain effective in nonsymptomatic patients. However, delaying treatment by just nine months introduces the risk of spinal cord compression. In their study, Crawford and co-workers [8] have shown that 45% of prostate cancer patients regarded quality of life as more important as opposed to 29% who stated a preference for prolonged survival. A trial carried...
out by Medical Research Council Prostate Cancer Working Party Investigator Group comparing early versus delayed treatment has recently been published [9]. For the first time the benefits of early treatment have been clearly demonstrated in terms of metastatic progression, complications, and deaths related to cancer.

Androgen Deprivation

Since the publication of the early works of Huggins in 1941 [10], the primary treatment for prostate cancer has been to stop testicular androgen production. This can be achieved by castration using estrogens such as diethylstilbestrol (DES) or more recently using antiandrogens (AAs) and luteinizing-hormone-releasing hormone (LHRH) agonists (monthly or every three months). This treatment decreases the plasma level of testosterone by 95%. Androgen deprivation, however, is associated with numerous possible side effects. These include decreased libido, impotence, hot flushes, anemia, hair loss, osteoporosis, fatigue, and psychological factors. The appearance of these effects markedly alters the patient’s quality of life.

Castration

Castration is either carried out surgically by bilateral orchiectomy or medically by LHRH agonists such as triptoreline, leuproreline, busereline, and gosereline. These treatments may sometimes induce a paradoxical effect usually described as a “flare-up.” This effect is more frequent in cases involving bone lesions and is due to initial, temporary increases in levels of LH and testosterone. These may lead to bone pains that last for about a week. This phenomenon explains the need for an AA that must be taken for two weeks before and after medical castration in order to avoid this flare-up effect.

Estrogens

For many years these agents have been regarded as the gold standards in androgen blockade. They influence the pituitary axis, adrenal secretion, and 5-alpha-reductase activity. They have played a very important role in hormonal therapy. However, DES does have its drawbacks due to its cardiovascular toxicity. As has been demonstrated in a study of veterans [11], the benefits obtained from 5 mg/d of DES appear to be countered by the reported side effects. These results have led to the use of lower doses of DES, even as low as 1 mg/d. These low doses have resulted in therapeutic benefits and reduced risk of cardiotoxicity in certain patients, even though it appears that the threshold dose of 3 mg/d is necessary to obtain total androgen blockade. In France, fosfestrol is widely used, mostly by i.v. administration [12]. Another estrogen is estramustine phosphate, which has the advantage of having both a hormonal steroidal component and a nitrogen mustard alkylating agent. The best known action of estramustine is the depolymerization of microtubules by interaction with tubulin. However, estramustine has also been demonstrated to have a cytotoxic action by binding to the nuclear matrix [13, 14].

Total Androgen Blockade

This concept, developed by Huggins in 1945, is based on the fact that the prostatic cells are androgen dependent and this is particularly so for dihydrotestosterone (DHT), a very active metabolite of testosterone. The production of this metabolite in the prostatic gland means that levels of androgen following castration vary between 20% and 40% of normal levels [15]. In fact, there are two pathways to bring about the transformation of testosterone into DHT. One route depends on the action of the enzyme 5-alpha-reductase that transforms testosterone into DHT. The other route involves production of dehydroepiandrosterone by the adrenal glands. This is converted to testosterone and then to DHT in the prostatic gland. The discovery that most metastatic prostate cancers are stimulated by androgens led to the search for and development of different means for their suppression. As a result of Huggins’ work [10], bilateral orchiectomy was long considered to be the standard treatment. More recently, estrogens, LHRH agonists, and AAs have emerged as newer treatment options.

Antiandrogens

The mode of action of the AAs results in the blockade of the androgen receptors of the prostate cells. There are two types of AAs: steroidal AAs and nonsteroidal AAs (NSAAs). Steroidal AAs induce a decrease in plasma levels of testosterone by slowing the release of pituitary LH and by partial inhibition of 5-alpha-reductase. Steroidal AAs include cyproterone acetate and megestrol acetate, which also block the cellular androgen receptors.

The NSAAs are more interesting from a clinical point of view because they are purely AAs acting mainly by inhibiting competition with the fixation of DHT on the androgen receptors. They do not reduce, and may even increase, the plasma levels of testosterone and this may have an impact on the libido of the patients. The NSAAs include flutamide, nilutamide, and bicalutamide.

Total Androgen Blockade

The association of AAs with an LHRH agonist such as leuprolide allows total androgen blockade (TAB) at both testicular and adrenal levels. Results of the first randomized National Cancer Institute study that took place in 1989 [16] were very encouraging. In this study, 603 stage 2 patients
were randomized between chemical castration with leuprolide and placebo or AA with flutamide. The results showed an improvement in the rate of progression (13.6 versus 16.5 months) and a marked improvement in global survival (28.3 versus 35.6 months), a gain of 7.3 months ($p = 0.035$) in the TAB group. These results, reported by Crawford and colleagues were later confirmed in 1993 by a European Organisation for Research and Treatment of Cancer (EORTC) study. At the same time, Denis and co-workers [17] reported a similar improvement in survival time of 7.3 months ($p = 0.02$), in favor of a combination of flutamide with LHRH agonist compared to orchietomy alone.

In 1995, Crawford [18], in a second study with 1,387 D2 patients treated with orchietomy and flutamide or placebo, did not find such a clear-cut difference in the decrease of PSA or in progression-free survival (33 versus 30 months). In the same year, a meta-analysis of 25 trials comparing castration alone to TAB [19] found no significant difference between the two treatments (five-year survival: 22.8% versus 26.2%; $p = 0.0512$).

The different means of achieving TAB do not appear to be equivalent. The long-term effects of using estrogens and LHRH agonists compared to bilateral orchietomy do not seem to be the same [20]. The trials that show a significant benefit with TAB in terms of survival are those where castration is medical and nonsurgical. It has been shown that estrogens and the LHRH agonists have a direct cytotoxic effect on prostate cancer cells [21]. Moreover, the association between LHRH agonists and AAs seems to have an additive if not synergistic effect. Indeed, investigations of receptors to LHRH [20] on immortal lines of prostate cancer cells (LNCaP and ALVA-31) have taken place. Results revealed that the combination of LHRH agonists with AAs has greater powers of inhibition than each one of them alone acting on androgen sensitive (LNCaP) or resistant lines (ALVA-31).

Caubet and colleagues [22] in a recent meta-analysis used rigid inclusion criteria that excluded nonrandomized studies and those studies where there is no NSAA. This meta-analysis included nine studies and established the benefits of TAB in terms of objective response as well as progression-free survival and overall survival (but without significant statistical difference). In the context of TAB, the use of LHRH agonists with NSAAs appears to be the better option.

Flutamide is the reference AA. A recent randomized study of 813 patients [15] compared flutamide with bicalutamide associated with an LHRH agonist. The results show progression-free survival and an identical survival at 95 weeks but with a better tolerance to bicalutamide, especially gastrointestinal (lower incidence of diarrhea) [23].

Intermittent Androgen Blockade

Several investigators [24] have suggested that hormone therapy be stopped when normalization of PSA level is achieved and that hormone therapy should be started again in case of relapse. The aims are to increase the quality of life of these patients and to delay the appearance of hormonal resistance. To justify this strategy, these investigators consider that apoptosis is hormone dependent and the tumor can grow even in the absence of testosterone. Certainly, this is linked to the selection of hormone-resistant clones, but genetic alterations may appear in this cellular-resistant population [25, 26]. Androgen (testosterone) production would allow a tumoral redifferentiation and reincrease the capacity of prostate cancer cells for apoptosis and so would retain hormonal dependence [27] and again effectiveness of androgen blockage. This approach would permit a better quality of life along with associated obvious economic benefits. As has already been mentioned, the Crawford study [8] has shown that patients prefer preservation of quality of life rather than prolonged survival (43% for preservation of quality of life, 29% for the prolongation of survival, and 13% for survival without progression). Conversely, physicians seem to focus on efficacy of treatment. M. Zerbib, in a personal communication, has reported that 25 out of 31 patients treated with intermittent androgen blockage, who were sexually active before the beginning of the treatment, rediscovered their sexual activity when hormonal therapy was stopped once the desired response had been achieved.

SECOND-LINE TREATMENT

AA Withdrawal

The need for second-line treatment, or the need to interrupt AA therapy [28] may follow failure of TAB. This may take place after an 18-month response to androgen deprivation. Three studies reported by Small [7] involving 139 patients on flutamide with progressive disease have indeed shown that simple withdrawal of flutamide brought a PSA decrease in about 21% of the cases, with a median response of 3.5 to 5 months. Patients who have a more extended response to flutamide are often those who respond to its withdrawal [29]. In cases of combination of flutamide with another hormonal treatment, the response seems more marked when this latter treatment was given at the start of flutamide rather than later (i.e., when flutamide seems less active). Thus, it seems logical to suggest the withdrawal of flutamide as a treatment when it has been used alone or in earlier association and especially when it has been used for a long period (more than 18 months). This phenomenon has a relationship with a possible amplification of the gene of androgen receptors.
and in general lasts about five months [36].

logical toxicity. The duration of response is usually short of objective response) but exhibits some renal and neuro-
ativated by the AAs or other steroid hormone as adrenal androgens [24].

Unfortunately, the benefit of withdrawal of AAs like flutamide, when seen, lasts only for a few months. This leads to the need for a new second- or third-line treatment. The choice of a new second- or third-line treatment is rather difficult since the criteria of evaluation and activity are difficult to standardize. This is due to the fact that 80%-90% of the patients do not have a measurable lesion. The major difficulties in considering the value of treatment are the large number of parameters to be taken into consideration (Table 1), the knowledge that evaluation criteria have changed over the years [30], and that they sometimes appear to be in conflict [31]. This was somewhat discouraging during the 1980s and could explain a renewed interest in the use of chemotherapy [32, 33].

Before deciding on the second- or third-line treatment, previous exposure to hormones must be considered as this can have an influence on the response to subsequent therapy. The difficulty in comparing prospective studies where evaluation criteria were often very different may help explain the wide range of different choices for second-line treatments: aromatase inhibitors, estrogens, chemotherapy alone, and hormone chemotherapy [34].

Androgen Deprivation

Surgical or chemical adrenalectomy with aminoglutethimide and hydrocortisone gives a less than 10% objective response. Similar response figures are obtained with ketoconazole, which needs high doses that are poorly tolerated [35]. Suramin may be more active (from 35% to 54% of objective response) but exhibits some renal and neurological toxicity. The duration of response is usually short and in general lasts about five months [36].

Estrogens

The estrogens could be more interesting, especially fosfestrol, which is less cardiotoxic than DES [37]. Fosfestrol has the advantage of being administered via an i.v. line and has a more rapid uptake. Because fosfestrol is a prodrug that is metabolized to DES in the cancer cells, it exhibits very low plasma levels and has low cardiotoxicity. Standard treatment with fosfestrol is 10 days' perfusion at incremental doses (from 1,200 mg on day 1 to 3,000 mg on day 5) followed by oral administration. Grise [12] reports a level of response of 40% (on the PSA level as well as on the quality of life), which may be a very important prognostic factor since the median survival of the responders is 19.6 months versus 4.2 months among the nonresponders. Similar results have been reported by other investigators with a median survival of around five months.

Sometimes, after progression under AA therapy followed by failure of estrogen, a new benefit related to AA therapy can be obtained. This is due to a redifferentiation of cancer cells by mutation of the androgen receptors [7]. Also, sensitivity to androgens can be noted [24]. The activity of antiestrogen therapy (tamoxifen) has also been noted. This may be explained by the possibility of the presence of estrogen receptors.

Antiaromatases

The inhibition of aromatase blocks the conversion of cholesterol in pregnenolone. Aminoglutethimide inhibits the biosynthesis of adrenal steroids as does ketoconazole at high doses. More recently, similar effects have been noted for lio-
prozole and liarozole [7]. Other aromatase inhibitors already used in advanced breast cancer such as letrozole or anastro-
zole are under study. At a similar level, low doses of steroids may be active by slowing the activity of the adrenals [7, 30].

Chemotherapy

If the treatments already described have failed, this is indicative of hormone refractory prostate cancer. This leads to the use of chemotherapy, but strict precautions must be observed with elderly patients. The first publications on chemotherapy go back some 20 years [32, 33], and success was evaluated in these studies using different criteria. This may help explain the discrepancies in the reported results [6].

Hormone refractory prostate cancer has long been considered to be a chemotherapy-resistant disease [38]. Indeed, no randomized study has been able to demonstrate the benefit of chemotherapy on survival rate [5, 6, 32]. Over the last 10 years, several nonhormonal agents have been shown to exhibit a certain efficacy when evaluated according to decrease of PSA. However, none of these studies had patient populations greater than 100 [6]. Consideration of the quality-of-life evaluation criteria has somewhat modified this situation. Thus, the results obtained by Tannock [39] confirm

Table 1. Criteria of evaluation of response to second-line treatment

- Level and minimal length of decrease of PSA levels (>50%, >80%, and for a defined period of time, i.e., eight weeks).
- Return of PSA to a level considered satisfactory (<4, <10 µg/ml).
- Minimum length of decrease of PSA levels to consider the presence of response (>8 weeks).
- Post-therapy changes in bone scan (intensity and number of foci).
- Isolated changes of measurable lesions or associated with other elements (PSA levels, bone scan).
- Scale of quality of life (pain relief, decrease in use of analgesics, performance status, weight).
- Survival without progression (with what criteria of relapse?).
- Global survival.
the interest of chemotherapy with respect to certain criteria (visual scale of evaluation of pain, performance status, and modification of weight).

A better evaluation of the classical drugs (vinblastine, cyclophosphamide, doxorubicin, mitoxantrone), the newer ones (cisplatinum, taxanes), or simultaneous combination with hormonal therapy (estramustine) or in sequential administrations [40] should be possible through phase III trials. This evaluation could consider quality-of-life criteria to be of the same level of importance as decrease in PSA, the prolongation of survival, and global survival.

Of the most widely studied drugs, the best results have been obtained with cyclophosphamide, doxorubicin, and mitoxantrone. Unfortunately, few studies exist and the new molecules are still being evaluated. However, it is already well recognized that the combination of antihormonal therapy, particularly with estramustine, increases the level of response (Table 2).

We must be very careful about the evaluation of responses to these drugs [31] and, as has already been mentioned, we must take into account previous treatments. For example, bicalutamide is more active following flutamide than following placebo [7]. Steroid therapy, which is used as an antiemetic with chemotherapy, gives alone about a 20%-40% response rate [39], and the interval of time since the end of the previous hormonal therapy must be considered for the withdrawal effect. The response to withdrawal usually happens within a month. Exceptions are nilutamide and bicalutamide, which have longer half-lives (response in eight weeks) [7]. Thus, in cases of response to hormonal therapy, we have to wait for the objective signs of relapse before starting with chemotherapy. Finally, it is important to be sure that the plasma levels of testosterone obtained are consistent with the levels associated with castration [6].

Hudes [41], in a randomized study of 192 patients on second-line treatment, has compared vinblastine alone versus vinblastine and estramustine. He has obtained measurable responses of 6% and 18%, respectively, a progression-free median survival of 1.9 and 3.7 months ($p = 0.001$) and a global survival of 9.2 and 11.9 months ($p = 0.18$). Although nonsignificant, this figure corresponds to an increase of 25% in global survival.

Even if chemotherapy has no impact on survival, it demonstrates benefits in terms of quality-of-life parameters [6, 42]. Tannock, in 1989, investigated steroid therapy [39] as

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### Table 2. Second-line treatment with medical therapy

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Response Rate (%)</th>
<th>PSA &gt; 50%</th>
<th>Objective</th>
<th>Stable</th>
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<tr>
<td>Cyclophosphamide</td>
<td></td>
<td>—</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Doxorubicin (20 mg/m²/week)</td>
<td></td>
<td>39</td>
<td>5–33</td>
<td>84</td>
</tr>
<tr>
<td>Doxorubicin + cyclophosphamide</td>
<td></td>
<td>—</td>
<td>46</td>
<td>—</td>
</tr>
<tr>
<td>Vinblastine</td>
<td></td>
<td>3</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td>—</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td></td>
<td>16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mitoxantrone + prednisone</td>
<td></td>
<td>20</td>
<td>—</td>
<td>52</td>
</tr>
</tbody>
</table>

<table>
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<th>Agents</th>
<th>Response Rate (%)</th>
<th>PSA &gt; 50%</th>
<th>Objective</th>
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<tr>
<td>Cyclophosphamide + prednisone + diethylstilbestrol (DES)</td>
<td>39</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Doxorubicin + ketoconazole</td>
<td>55</td>
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**Estramustine:**

<table>
<thead>
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<th>treatment</th>
<th>Response Rate (%)</th>
<th>PSA &gt; 50%</th>
<th>Objective</th>
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<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+ Vinblastine (VLB)</td>
<td>25–54</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+ VLB/doxorubicin + ketoconazole</td>
<td>67</td>
<td>75</td>
<td>—</td>
</tr>
<tr>
<td>+ Etoposide</td>
<td>58</td>
<td>46</td>
<td>—</td>
</tr>
<tr>
<td>+ Paclitaxel</td>
<td>53</td>
<td>28</td>
<td>—</td>
</tr>
<tr>
<td>+ Paclitaxel + etoposide</td>
<td>52</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+ Docetaxel</td>
<td>62</td>
<td>31</td>
<td>—</td>
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</tbody>
</table>
second-line treatment. In a randomized study [42] of 161 patients he compared prednisone alone (10 mg/d) versus the combination of prednisone and mitoxantrone (12 mg/m²/3 weeks). This followed the results of a phase II study [43] showing activity and good tolerance. A significant benefit of the chemotherapy was demonstrated in terms of objective response (29% versus 12%), median responses (43 weeks versus 18 weeks), and global palliative benefit (38% versus 21%). Among patients in failure with prednisone alone, the association with mitoxantrone gave a 22% response rate (with a median of 18 weeks). Global survivals were identical, with a median of 11 months, but 50 out of 80 patients treated with prednisone alone relapsed and then received mitoxantrone. This treatment was associated with improvement in pain relief and global quality of life. The global quality of life was very significantly improved by mitoxantrone and lasted longer according to two different methods of evaluation (EORTC QLQ-30 and QOLM-P14, a trial-specific module) [44]. Moreover, tolerance was very good with only two cardiac failures recorded among the 130 patients (average age 68 years) taking mitoxantrone.

Ellerhorst [40] has described another approach that has shown very interesting results. In his study of 46 patients resistant to flutamide, he employed a regimen of alternated hormone-chemotherapy (one week with doxorubicin and ketoconazole, and the other with vinblastine and estramustine) combined with daily hydrocortisone. On measurable lesions (soft tissues), he has obtained 75% response (12 out of 16), a decrease of the levels of PSA of more than 50% among 67% of the patients (38 out of 46) and a decrease of more than 80% among 52%, and an improvement in the quality of life among 76%. The median response has been 8.4 months with an interesting global survival of 19 months. He has confirmed the prognostic value of the response (at 18 months, 64% of the responders are alive versus 35% of the nonresponders). Because of these promising results and the good tolerance, a phase III study has been started for hormone-sensitive forms. The association of two inhibitors of microtubules such as vinblastine and estramustine have already proved their activity [41].

A Japanese study has obtained similar results (8 objective responses out of 14, and a median survival of 18 months) with an association of interferon-α-2a at low doses and 5-fluorouracil with good tolerance. Unfortunately, the study involved insufficient numbers of patients to provide conclusive evidence [45].

PALLIATIVE THERAPY FOR PAINFUL METASTASES

Although external radiotherapy is the best treatment for pain related to localized bone metastases, i.v. bisphosphonates exhibit considerable activity against pain in diffuse bone lesions. These compounds act rapidly [46] and are nontoxic.

Biphosphonates

Biphosphonates do not themselves have any antitumor activity and only have a secondary role to play in the treatment of prostatic cancer. They act on the osteoclastic hyperresorption linked to the coupling of activity of bone cells (osteoblasts and osteoclasts). Clodronate and pamidronate have shown some analgesic activity and are of interest only in cases when usual treatments have failed [46].

External Beam Radiation

Radiotherapy is the mainstay of treatment for the nondiffuse painful metastases. These occur in about 85% of progressive, hormone-resistant cancers. Short, localized external beam irradiations (20 Gy in five fractions over one week or, more often, 30 Gy in 10 fractions over two weeks) bring partial or total pain relief in 80% of patients with negligible morbidity. Complete responses were most often found in patients with prostate cancer in comparison to other tumors [47]. Irradiations by large hemibody fields (6 Gy for the upper half of the body and 8 Gy for the lower half) are also efficient in relieving pain in about 75% of cases, with relief lasting several months. About 40% of patients responded within 48 hours [48].

Strontium 89

The preferential fixation of certain radiopharmaceutical isotopes on the bones, especially at points of growth, led initially to the use of phosphorus 32 in multifocal bone lesions. Because of its severe myelotoxicity, this agent has been largely replaced by strontium 89 or by other radioisotopes such as samarium 153 and rhenium 186 [49]. Strontium 89 is a pure β-emitting radionuclide that follows the same pathways as calcium and induces an almost total disappearance of bone pain between 10% and 50% of patients and partial disappearance in approximately 50% of the patients. It is associated with moderate blood toxicity (thrombocytopenia from four to eight weeks after the injection), but a possible benefit in terms of global survival has not been proven yet. Nevertheless, its combination with other products or techniques may be promising. In fact, strontium 89 combined with localized external irradiation, although not modifying survival, is associated with a decrease in the biological markers throughout the half-life of strontium. The use of cisplatinum (CDDP) in association with strontium 89 is especially interesting since CDDP reduces the possibility of repair of the radio-induced sublethal lesions. It has been seen that low doses of CDDP after low doses of strontium 89 have an obvious effect in terms of pain relief and in the decrease of disease markers without toxic effects [50].

Strontium 89, at the usual dose of 30 to 60 MCi/kg, after failure of medical treatment induces an improvement in
terms of pain relief that lasts several months in more than 50% of cases. Some investigators [49] have noted a benefit in survival. However, strontium 89 may induce transient increases in bone pain or flare-up within the first few days of administration. There is also the possibility of thrombocytopenia grade III to IV in more than 20% of cases. It is highly advisable to employ steroids during at least the first month of treatment. Samarium 153, a new radionuclide at a dose of 1 mCi/kg, induces pain relief in 62%-72% of patients with no instances of grade 4 and, rarely, grade 3 myelosuppressive toxicity [51].

**Advice on Treatment Selection**

Metastatic prostate cancer must be treated as quickly as possible. This is because of the risk of complications, particularly spinal cord compression, increases with time. Another factor is the recognition that patients in general appear to favor quality of life rather than length of survival. A recent randomized study shows a significant benefit of early treatment compared to delayed treatment based on the evolution of the disease, its complications, and the survival related to prostate cancer [9].

Androgen blockade is the treatment of choice, but should it be total (TAB) or selective? For TAB, which AA should be used? Castration may be surgical (bilateral orchietomy) or medical with LHRH agonists (all the different agonists have the same activity). The first option has the advantage of its simplicity, its moderate cost, and its permanence. The second approach provides the psychological comfort of temporary castration. Several studies have shown the superiority of TAB [16, 20, 22, 52] over medical castration alone. The non-steroidal AA cyproterone acetate has never shown any benefits in survival when associated with medical castration [53]. Surgical castration seems to diminish the benefit of TAB [18].

Intermittent treatment is still under investigation. The first clinical results indicate that it may delay the occurrence of hormone resistance [24] and that it is not a harmful method (M. Zerhbi, personal communication). In cases of progression under AA treatment, its withdrawal may bring about a 20% response (decrease of the values of PSA >50%). This effect has been observed with various AAs including not only flutamide but also bicalutamide and megestrol acetate [7]. However, the possible benefit lasts only a few months, raising the question of a second-line treatment: new AA, aromatase inhibitors, estrogens, or chemotherapy.

Bicalutamide, as a single agent (>150 mg/d), is active after the failure of flutamide but the contrary has not been proven [23]. The activity of megestrol acetate is very weak [7] and less interesting than the aromatase inhibitors. The association of aminoglutethimide with hydrocortisone is well tolerated and gives an approximate 50% response rate [54]. More recently, the combination of ketoconazole with hydrocortisone has been proven to be very active following the withdrawal of AAs [7]. This provides a dramatic improvement of the quality of life and, when associated with mitoxantrone, a positive effect has also been obtained [42]. Low doses of steroid therapy alone are active as well [39].

Estrogens like i.v. fosfestrol have the advantage of rapid activity especially as pain killers [12]. Estramustine is also active and is often associated with chemotherapy [41]. Its mechanism of action provides inhibition of microtubules (vinblastine, paclitaxel, etoposide), but the side effects in elderly patients are worse than those seen with mitoxantrone [31, 40]. In Tannock's randomized study, this drug provided a very significant improvement to steroid therapy in terms of response and in terms of quality-of-life criteria, particularly because of its very good tolerance [42]. The use of chemotherapy at low doses alternated or associated with various hormonal agents is another possibility. Ellerhorst [40] has reported on some very interesting results in terms of duration of response (8.4 months) as well as on global survival (19 months), but also an incidence of 49% of peripheral edema and 18% incidence of venous thrombosis linked to estramustine. Consideration could be given to a therapeutic protocol based on the same concept but of reduced toxicity by including in Tannock's protocol vinblastine alternated with mitoxantrone combined with i.v. fosfestrol.

In cases of multiple painful bone lesions, the therapeutic approach is rather different. Strontium 89, apart from its myelosuppressive effect (essentially thrombocytopenia), is well tolerated (steroid therapy is mandatory) with an obvious benefit in terms of quality of life [49]. It also has the advantage that it may be repeated after three to four months. Samarium 153 could be more active on painful lesions and less toxic than strontium 89 [51]. In cases of a single painful bone lesion, localized external beam radiotherapy is highly effective, with pain relief occurring in 80% of patients [48].

The choice of second-, third-, or even fourth-line treatment is difficult and must be based on the clinical response of the patient and the precise evolution of the disease. It is important to realize that clinical reports concerning the response rates to different treatment regimens vary widely since evaluation criteria differ considerably from one study to another [29]. The usual criteria to be considered are PSA levels (decline in PSA of 50%), measurable lesions (sum of the products of diameters of all measured lesions), activity against pain (measured by a visual-analog scale or analgesic consumption), change in weight, quality of life, and global survival. Among young patients or patients whose hormone refractory disease developed quickly, there is a tendency to start chemohormone therapy as a second-line
treatment (estramustine). For the other patients, aromatase inhibitors or estrogens (fosfetrol) are commonly employed, but single steroid therapy can still be an alternative. In case of failure or in the presence of painful bone lesions these treatments may be exchanged, replaced, or combined with external beam radiotherapy or strontium 89 or samarium 153. In all the cases the balance between tolerance and effectiveness must be maintained.

**CONCLUSION**

Over the last few years, important changes have taken place in the management of metastatic prostate cancer. TAB seems to bring benefits if castration is medical and the androgen is nonsteroidal, but must TAB be permanent or intermittent in order to improve quality of life without modifying the vital prognosis? There is an ongoing clinical trial that will try to answer this question.

**REFERENCES**


