Current evidence about intermittent androgenic deprivation in prostate cancer

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Abstract
Objectives: To identify clinical application of intermittent hormonotherapy in prostatic carcinoma.

Material and methods: We conducted a systematic review in the MEDLINE database and COCHRANE Library using the words MeSH “prostate cancer, androgenic deprivation and intermittent”. Those with the highest level of evidence and published in the last 10 years were included.

Results: Intermittent hormone therapy is one of the tools we use in urological armamentarium for special circumstances. This analysis highlights: possibility to regain sexual function during the period of suspension of treatment (time off) due to the recovery of testosterone levels also demonstrating an improvement in symptoms, decreased costs while preserving the same oncological control as compared to complete androgenic deprivation.

Conclusions: There is still controversy about the benefits in quality of life and the emergence of long-term side effects typical of continuous hormonal therapy. Therefore and until now, we should only propose intermittent therapy in selected patients.

Evidencia actual acerca de bloqueo hormonal intermitente en cáncer de próstata

Resumen
Objetivos: Revisar la aplicación de la hormonoterapia intermitente en el cáncer de próstata.

Material y método: Se realizó una revisión sistemática en la base de datos de MEDLINE y COCHRANE utilizando las palabras MeSH (Medical Subject Headings) “prostate cancer, androgenic deprivation e intermittent”. Fueron incluidos aquellos con el mejor nivel de evidencia, que han sido publicados en los últimos 10 años.

Resultados: La hormonoterapia intermitente es una de las herramientas del armamento urológico que utilizamos en circunstancias especiales. De este análisis se destaca: la posibilidad de poder recuperar la función sexual durante el periodo de suspensión del tratamiento (time off) debido a la recuperación de los valores de testosterona manifiestando además una
Introduction

Recently, the American Cancer Society reported that prostate cancer (PCA) is the second most common cancer diagnosed today and the sixth leading cause of death in men, with an incidence of 903,500 new cases annually. Urologists are living in a constant debate in terms of its controversial method of screening and its difficult treatment.

During diagnosis, the great majority are located and the treatment, in these cases, remains the surgical one although we have other alternatives such as radiotherapy, brachytherapy, ablative therapy, and active surveillance among others.

However, in patients with metastatic PCA, the standard treatment is hormone blockade (HB). Its pioneers were Huggins and Hodges, who, in the early 1940s, showed excellent results obtained with orchietomy in patients with metastatic and symptomatic PCA, finding that triggered his award with the Nobel Prize in 1966. This treatment is currently the standard treatment, leading to an objective and symptomatic response in approximately 80% of the patients. However, it is associated with non-negligible side effects including hot flashes, loss of libido, erectile dysfunction, cognitive dysfunction, fatigue, depression, osteoporosis, gynecomastia, anemia, loss of muscle mass, and metabolic syndrome that increases the risk of cardiovascular events. This was the reason why there is the concept of intermittent androgen deprivation (IAD) based on alternating periods of hormonal therapy and castration of treatment, allowing for hormonal recovery and, thus, reducing unwanted side effects, delaying also the condition of hormone refractory cancer as a final stage of the natural history of the disease. This phenomenon was well-demonstrated in a preclinical study published by Bruchovsky et al. where they found a 500-fold increase in androgen-independent cells in proportion to 20 times androgen-dependent cells after castration in animal models (Shionogi mice). Akakura et al. also showed that the period of progression to an hormone refractory-PCA was 3 times higher for the IAD than for the continuous. Apparently, androgen suppression in some moment and due to unknown causes would lead the prostate stem cell to a state of hormone insensitivity; therefore, disrupting the androgen suppression ‘temporarily’ would help keep the tumor sensitive.

In light of the evidence in preclinical studies, there is the concept and debate on the IAD, the reason why it stimulated the development of clinical studies on the subject. In this sense, Klotz et al. were the ones who developed and published the first clinical study in 1986 using the IAD as a treatment. It consisted in the discontinuation of diethylstilbestrol in patients with metastatic PCA after manifesting an objective clinical response to the treatment. Once the patients began again with the symptoms resulting from PCA, the treatment was restarted again, reporting a rapid clinical response again. These results stimulated the development of new works on IAD in different centers.

However, what is the current evidence on this treatment schedule and what is the statistical and scientific weight of the publications in the literature? Therefore, our goal is to communicate the results obtained from a systematic and critical review of the best publications to date on intermittent androgen deprivation in prostate cancer.

Acquisition of evidence

We conducted a systematic review in the MEDLINE database and COCHRANE using the words MeSH (Medical Subject Headings) ‘prostate cancer, androgen deprivation, and intermittent’. We included those with the best level of evidence, which have been published in English and in the last 10 years.

Synthesis of evidence

The oncologic benefit of continuous androgen deprivation (CAD) for the treatment of metastatic PCA remains palliative, as the disease will inevitably become hormone-resistant (24 months). Moreover, during the treatment period, the patient is not free from the side effects typical of androgen deprivation. Therefore, the CAD would serve at least three benefits to the patient with a metastatic PCA; possibility of restoring the sexual function during the period of discontinuation of the treatment (time off) due to the recovery of testosterone values besides manifesting symptom improvement; reduction of costs and, the most important one, presenting the same oncological control as compared to the CAD.

There are several hypotheses to explain the possible use of intermittent hormone therapy as well as the manner and time of application.

Basically, the aim of IAD is to improve the quality of life in patients with metastatic PCA with oncologic outcomes equal to or better than the CAD.

The results of phase-2 studies are biased, because their designs were very heterogeneous, with patients rolled in different stages of the disease, and with different values of the prostate specific antigen (PSA) that determined the discontinuation of the treatment, changes in the time of each cycle, and treatment regime; which is why it is difficult to make a comparison without biases. Recently, Abrahamson published a systematic and thorough review on IAD and its effectiveness in the treatment of PCA. With regard to the phase-2 studies, the author concluded that although the...
treatment has potential benefits in terms of the tolerability thereof, phase-3 studies are required to show which patients would benefit from this treatment schedule, what would be the response rate and especially if there are survival benefits. This is the reason why we mention particularly those phase-3 studies published to date. Calais da Silva et al. developed a randomized and prospective phase-3 study of the South European Urological Group (SEUG) in which a total of 626 patients divided into 2 groups were randomized: 314 who were treated with IAD and 312 with CAD. In this trial, we evaluated as a primary objective, the time to subjective or objective progression of the disease and, as a secondary one, the survival and quality of life. In addition, the time without treatment (time off) was also recorded in the group under the CAD scheme. The inclusion criteria were those patients with clinical stage cT3–cT4 M0, cT3–cT4 M1, PSA greater than or equal to 4 ng/ml, less than 80 years age, and performance status 0–2 (WHO). All the patients underwent induction therapy for 3 months with cyproterone acetate 200 mg for 2 weeks followed by monthly injection of an LHRH analog depot plus cyproterone in doses of 200 mg daily. Those patients with PSA value lower than 4 ng/ml or a decrease greater than 80% of the PSA value compared to the start of the treatment were randomized. The patients randomized to the group under IAD ceased the treatment and those to continuous treatment received 200 mg cyproterone daily plus the LHRH analog. In group 1, the therapy was again restored when the PSA increased to greater than or equal to 10 ng/ml in symptomatic patients or greater than or equal to 20 ng/ml in asymptomatic patients. 40.4% (127 of 314 patients) progressed from the group with IAD and 34.3% (107 of 312) of the CAD group. There were no statistically significant differences in survival describing 170 and 169 deaths in groups 1 and 2; respectively. The side effects of the treatment were more frequent in group 2 with higher number of deaths from cardiovascular disease (52 versus 41). In addition, the patients treated with IAD referred better sexual function. Finally, the median time without treatment in group 1 was 52 weeks (95% CI: 39.4–65.7). Against this study, the authors concluded that the IAD should be taken into consideration as it is not associated with lower survival or clinically significant impairment in quality of life, with better sexual function and even economic benefits. De Leval et al. had previously published another study but with fewer enrolled patients (68 patients) divided into 2 groups: 33 with CAD and 35 with IAD. They were evaluated as the primary outcome of the time to develop a hormone-resistant PCA. Both groups were homogeneous. The estimated rate of progression at 3 years was significantly lower for the group with IAD (7% ± 4.8%) versus the group with CAD (38.9% ± 11.2%, p = 0.0052). The authors concluded that the IAD could keep the PCA hormone-resistant for a longer period of time. However, the limitations of this publication are the short follow-up (30.8 months) and the few patients enrolled. Recently, Langenhuijzen et al. developed a prospective and randomized study comparing CAD versus IAD in patients with metastatic PCA. They evaluated the pretreatment PSA value as a predictor for progression and the role of the dynamics of testosterone on the quality of life. Although the inclusion criteria were similar to those published phase-3 studies, the induction period was longer (6 months) and they used different drugs for the central and peripheral androgen deprivation. The result they obtained was that in patients with metastatic PCA and high PSA levels prior to androgen deprivation or pain, they had a worse prognosis. In addition, those patients with IAD and low nadir PSA had a higher progression rate compared with CAD. While they reported more side effects in patients with CAD, they found no greater benefits in quality of life between the two treatment schemes. They explained this phenomenon with the finding that the testosterone values remained in castration values after discontinuation of treatment during the IAD and that did not quite recover before restarting the deprivation. That is why; the authors concluded that the IAD is not a good treatment option for many patients with metastatic PCA.

In recent years, various revisions were published in the literature attempting to clarify the role of IAD in metastatic PCA. Prapotnich et al. in their publication, also based on the experience of the Instituto Montsouris, concluded that the IAD must currently be considered a safe and reliable treatment for metastatic PCA except in patients with severe metastatic disease or a PSA value above 100 ng/ml before the treatment initiation. However, in this review, publications that demonstrated the survival rate with IAD compared to the CAD were not selected. In 2007, the Cochrane group published another systematic review of 5 randomized controlled trials in which there was a flaw in the patients under IAD as far as survival is concerned, a reason why we could not reach a conclusion on the IAD role in metastatic PCA. A more thorough review was conducted by Abrahamsson evaluating more variables such as quality of life, efficacy, and tolerability of the IAD. In this comprehensive and systematic review, the author concluded that the IAD appears to be as effective as the CAD with the advantage of greater benefits in the quality of life and tolerability, especially in the recovery of sexual potency. However, data to determine whether the IAD has the potential to prevent those long-term side effects observed with the CAD are still lacking. Finally, Buchan and Goldenberg recently published another review concluding that the IAD offers significant benefits in the quality of life, particularly on sexual function during the periods without treatment (time off). Furthermore, it is not lower than the CAD regarding the survival and the time of progression to hormone resistance.

The IAD appears to be a good option in the metastatic PCA; however, which patient might benefit from this treatment. In this connection, Crook et al. suggest in their publication that patients with local or biochemical recurrence after radiotherapy could benefit with IAD because they are free of treatment for extended periods being still less possible to develop a hormone-resistant PCA. De Leval et al. showed that the IAD was higher than the CAD in patients with poorly differentiated PCA or in those with no evidence of bone metastases. However, De la Taille et al. revealed that the patients candidate to IAD are those older than 70 with localized PCA, Gleason score lower than or equal to 7, and when the period without treatment was longer than 1 year. Some publications have determined criteria for patients who would not be candidates for IAD such as bulky tumors, with numerous lymph nodes or bone metastases, PSA doubling time shorter than 9 months, and early PSA value above 100 ng/ml or severe pain.
Currently, intermittent androgen deprivation remains controversial despite the published studies. The update of the European Guidelines of Urology (EAU) was recently published, in which it is considered that the PSA threshold remains empirical, on which androgen deprivation should be discontinued and continued, that the induction cycle should last between 6 and 9 months, that the treatment should be stopped when there is a real response in the PSA value (lower than 4 ng/ml in patients with metastatic PCA or 0.5 ng/ml in patients with relapse) and restored when there is clinical progression or when the PSA value goes above an empirically set threshold (usually 4 ng/ml in non-metastatic patients and 10–15 ng/ml in metastatic situations). Furthermore, the treatment is maintained in the same manner as the induction cycle, between 6 and 9 months depending on the time required to reach a PSA nadir. Therefore, they conclude that the IAD should not be considered an experimental treatment despite the lack of randomized clinical trials with long-term follow-up (Level of Evidence 2). In this connection, 2 multicenter randomized trials are being conducted (NCIC PR7 and SWOG 9346), trying to determine the benefits in terms of quality of life of the IAD over the CAD and over the prevention of occurrence of side effects in the long term.

Conclusion
The current evidence has set the intermittent androgen deprivation in the treatment options for metastatic or recurrent prostate cancer after the primary treatment. Mainly, it would be indicated as an option in patients with recurrent primary treatment or metastatic prostate cancer; however, those with bulky tumors, large number of bone metastases, severe pain, or PSA value at baseline greater than 100 ng/ml would not benefit from it.

The benefits on the quality of life and the emergence of long-term side effects of continuous androgen deprivation are still controversial. Therefore and for now, we should only provide intermittent therapy in selected patients.

Conflict of interest
The authors declare that they have no conflict of interest.

References