Intermittent androgen deprivation therapy and its association with reduced castration resistance in patients with prostate cancer

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KEYWORDS
Prostate cancer; Androgen blockade; Castration resistance; Mexico.

Abstract
Background: Androgen deprivation therapy (ADT) has been considered the treatment of choice for prostate cancer. For reasons still unknown, on an average of 24 months, this tumor is characterized by androgen-independent growth. It has therefore been proposed that intermittent androgen deprivation (IAD) could stop the tumor from progressing to androgen insensitivity.

Aims: The aim of the present study was to look for the association between IAD and a decrease in castration-resistant disease.

Methods: A retrospective, analytic, case-control study was conducted. Ninety-one patients diagnosed with prostate cancer and treated exclusively with ADT from the onset were analyzed. They were divided into 2 groups. Group 1 was made up of 39 patients managed with IAD. Group 2 consisted of 52 patients managed with continuous androgen deprivation (CAD). Odds ratio (OR) was determined and statistical significance was set at a \(p<0.05\).

Results: There was a reduced risk for developing castration-resistant disease in the IAD group (OR=0.31, 95%CI=0.038-2.5), but with a \(p=0.25\), which was not statistically significant.

Discussion: When IAD was used, the risk association analysis suggested a tendency, although not statistically significant, toward a lower probability of both developing castration-resistant disease and having a fatal outcome.

Conclusions: IAD did not significantly reduce the risk for castration-resistant disease.
Resumen

Introducción: La terapia de bloqueo androgénico (Ba) ha sido considerada el tratamiento de elección para cáncer de próstata. Por razones desconocidas, con un promedio 24 meses, el tumor se caracteriza por el crecimiento independiente de andrógenos. Por lo anterior, se ha propuesto que el Ba intermitente podría impedir la progresión del tumor hacia la insensibilidad a los andrógenos.

Objetivo: Buscar la asociación del Ba intermitente con la disminución de resistencia a la castración.

Material y métodos: Estudio analítico, retrospectivo, de casos y controles. Se analizaron 91 pacientes con diagnóstico de cáncer de próstata tratados sólo con Ba desde un inicio, se dividieron en 2 grupos: uno conformado por 39 pacientes, el cual se manejó con Ba intermitente; y el otro, conformado por 52 pacientes bajo manejo con Ba continuo. Se determinó razón de Momios (RM), con valor significativo establecido a \( p < 0.05 \).

Resultados: Se evidenció una disminución del riesgo de desarrollar resistencia a la castración en el grupo con Ba intermitente (RM = 0.31; intervalo de confianza, IC 95% = 0.038-2.5) pero con \( p = 0.25 \), lo cual no es estadísticamente significativo.

Discusión: El análisis de asociación de riesgos sugiere una tendencia, aunque no significativa, a una menor probabilidad de desarrollar resistencia a la castración, así como de un desenlace fatal, cuando se utiliza Ba intermitente.

Conclusión: El Ba intermitente no mostró disminuir significativamente el riesgo de resistencia a la castración.

PALABRAS CLAVE
Cáncer de próstata; Bloqueo androgénico; Resistencia a la castración; México.

Introduction

Androgen deprivation therapy (ADT) has traditionally been regarded as the treatment of choice for advanced or metastatic prostate cancer, but there are numerous other settings in which ADT is used.¹

ADT as the sole therapy for localized prostate cancer is currently gaining in popularity.²,³ In a recent publication, Smith emphasized that out of 2 million men diagnosed with prostate cancer in the United States, approximately 600,000 (30%) receive ADT.⁴

Beyond the effects on quality of life, the suppression of testosterone production has been associated with various severe adverse effects called androgen deprivation syndrome.⁵ Among them are loss of libido, erectile dysfunction, fatigue, osteoporosis, hot flashes, insulin resistance, cerebrovascular events, dyslipidemia, and metabolic syndrome.⁶-¹²

More importantly, and for reasons unknown, the process of cell death induced by androgen ablation fails to eliminate the entire malignant cell population and after a viable period with a mean of about 24 months, the tumor inevitably recurs and is characterized by androgen-independent growth.¹³ Therefore it has been proposed that intermittent androgen deprivation (IAD) could impede the progression of the tumor into androgen insensitivity.¹⁴

IAD does not lead to a greater risk for death than that in patients with continuous androgen deprivation (CAD) and should be considered standard prostate cancer therapy. Nevertheless, patients with advanced disease, a high Gleason score, and high pretreatment levels of prostate-specific antigen (PSA) do not show adequate biochemical PSA response to androgen deprivation and should not be regarded as candidates for IAD.¹⁵

The most recent articles in the medical literature state that the early use of ADT reduces the risk for metastasis at 10 years by 30%, but not castration-resistant disease or death by cancer, compared with differed androgen deprivation.¹⁶ The aim of the present study was to associate IAD with a reduction in castration-resistant disease in patients with prostate cancer.

Methods

An analytic cross-sectional study was conducted at the Hospital Regional Lic. “Adolfo Lopez Mateos” of the ISSSTE. The case records were reviewed of 134 patients diagnosed with localized or locally advanced prostate cancer within the time frame of 2005 to 2012 that had received ADT for any reason. A total of 91 patients had complete clinical case records. The inclusion criteria were prostate cancer diagnosis detected through transrectal prostate biopsy, any Gleason score, clinical stage T1-4 N0-1 M 0 disease, and any PSA value. All patients with incomplete case records or that had undergone previous radiotherapy were excluded.

All the patients received initial ADT with luteinizing hormone-releasing hormone (LHRH) analog every 3 months and 50 mg bicalutamide daily the first 15 days, once the PSA...
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For their analysis, the patients were divided into 2 groups, each one with adequate response to the initial treatment. Group 1 was made up of 39 (42.8%) patients; they were managed with idAD, with its transitory suspension when the PSA nadir was reached, reinitiating the aDT when PSA increased to 4 ng/mL. Group 2 was made up of 52 (57.1%) patients that were managed with CAD.

The patients had a 12-week follow-up and the criteria used for defining castration resistance were those recommended by the 2013 European Urology Guidelines. The patients presenting with castration-resistant disease were referred for chemotherapy. The Student’s t test was used for the parametric variables and the level of significance was set at \( p < 0.05 \). Odds ratio (OR) was used along with the SPSS® version 19 statistical program.

Results

Ninety-one patients were included in the study and divided into 2 groups whose baseline characteristics are shown in Table 1.

The mean follow-up period for the idAD and CAD groups were 49.6 months (range 8-156) and 45.29 months (6-192), respectively, with a \( p = 0.60 \).

Castration-resistant disease was documented in one case of the idAD group at 18 months, whereas 4 patients of the CAD group presented with it at a mean 10.5 months. The OR of castration resistance was 0.31, 95% confidence interval (CI) 0.038-2.5, with a \( p = 0.25 \).

Three deaths were registered in the study; one patient from the idAD group and 2 patients from the CAD group, these last 2 due to causes directly related to the cancer (OR=0.67; 95%CI=0.05-7.67; \( p = 0.61 \)).

Discussion

The analysis of the risk association suggested a tendency, although not significant, towards a lower probability of developing castration-resistant disease and fatal outcome with the use of idAD.

The lack of statistical significance was very likely due to the small sample size and the descriptive study design, and therefore the results should be interpreted with caution.

We do not propose that idAD is superior to CAD, but rather that both treatments are equally safe and efficacious in the treatment of localized and locally advanced prostate cancer, with the difference that idAD has a lower cost and fewer side effects than CAD.

It is interesting that the period of ADT treatment commencement to the presentation of castration resistance was longer in our study than that of the mean 24 months reported in the literature. The majority of the patients in our study, at a mean 46.28 months of treatment, have not presented with castration-resistant disease.

Conclusions

IAD did not show a statistically significant decrease in the risk for castration-resistant disease.

Conflict of interest

The authors declare that there is no conflict of interest.

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References


