

A HEPATOTOXICITY STUDY REGARDING BONE METASTASATED PROSTATE ADENOCARCINOMA HORMONOTHERAPY

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Abstract

The aim of the present study was to establish which therapeutical scheme used in the hormonotherapy (HT) of metastasated prostate adenocarcinoma at bone level was less hepatotoxic, on long-term therapy (period of 4 years). For this purpose, the levels of serical transaminases activity at well established time intervals have been determined, throughout the hormonotherapy period and after the hormonotherapy was stopped due to hepatotoxicity. Usually, for treating metastasated prostate adenocarcinoma, a combined hormonotherapy is necessary. Flutamide and cyproterone are synthetic substances for the treatment of metastasated prostate adenocarcinoma that bind to androgen receptors and block the cellular effects of circulating testosterone and dihydrotestosterone (androgen receptor antagonists). The most incriminated in generating hepatotoxicity is the combined therapy with Flutamide, the incidence being more elevated than in Flutamide monotherapy. Cyproterone is also incriminated in unleashing hepatotoxicity. In the case of Cyproterone the incidence of generated hepatotoxicity was the same for combined and mono-hormonotherapy.

Rezumat

Obiectivul studiului, desfășurat pe o perioadă de 4 ani, a fost stabilirea schemei terapeutice optime pentru hormonoterapia adenocarcinomului de prostată metastazat la nivel osos, în vederea evitării hepatotoxicității terapiei. În acest scop s-a determinat activitatea transaminazelor serice la intervale bine stabilite de timp, pe întreaga durată a hormonoterapiei și în urma stopării hormonoterapiei datorită hepatotoxicității. În general, în tratamentul adenocarcinomului de prostată este necesară utilizarea unei scheme terapeutice complexe. Flutamidul și ciproterona sunt substanțe de sinteză, utilizate în terapia adenocarcinomului de prostată metastazat, compuși ce acționează prin blocarea receptorilor androgenici. Flutamidul este cel mai incriminat în apariția hepatotoxicității, incidența fiind crescută în cazul terapiei combinate, comparativ cu monoterapia. Și ciproterona este incriminată în apariția hepatotoxicității, aceeași incidență prezentând atât terapia combinată cât și monoterapia.

Keywords: hepatotoxicity, hormonotherapy (HT), alanin-aminotransferase (ALT), aspartat-aminotransferase (AST)

Introduction

More than half a century ago, hormone use was instituted as the cornerstone treatment for advanced prostate cancer, and it continues to be the mainstay of therapy for this disease [1, 2, 10].

Still, it is known that nonsteroidal antiandrogens have different tolerability profiles [11]. Flutamide for example, is associated with diarrhoea and liver toxicity [3-5], while bicalutamide is better tolerated. [6]

Also, disturbances of liver function have been reported among long-term cyproterone users [7-9].

Materials and methods

The study was performed at the National Oncologic Institute "I. Chiricuță" Cluj-Napoca, for a period of 4 years. There have been studied 8 groups, 35 patients each, diagnosed with bone metastases ($M_{1b(bone)}$) prostate adenocarcinoma, with a Gleason score 7-10, aged between 60-70 years. Gleason score system is based on microscopic tumor patterns and points the degree of loss of the normal glandular tissue architecture. It is a number ranging from 2 to 10.

Thus, the studied groups were:

- Group I – combined therapy: bilateral orchiectomy (BO) followed by Flutamide (Fluta) hormonotherapy: 3x1tablet/day (250mg/tablet)
- Group II – combined therapy: bilateral orchiectomy followed by Bicalutamide (Bica) hormonotherapy: 1tablet/day (50mg/tablet)
- Group III – combined therapy: bilateral orchiectomy followed by Cyproterone (Cypro) hormonotherapy: 2x2tablets/day (50mg/tablet), at 12 hours interval
- Group IV – combined therapy: Flutamide+Goserelin (Fluta+Gose) hormonotherapy, simultaneous administration. Flutamide: 3x1tablet/day (250mg/tablet), at 8 hours interval and Goserelin (Gose): 3.6mg/28 days, subcutaneously administered in the abdominal wall region
- Group V – monotherapy: Leuprolide (Leupro) hormonotherapy: 3.75 mg/28 days subcutaneously administered in the abdominal wall region
- Group VI – monotherapy: Flutamide (Fluta) hormonotherapy: 3x1tablet/day (250mg/tablet), at 8 hours interval
- Group VII – monotherapy: Bicalutamide (Bica) hormonotherapy: 1tablet/day (50mg/tablet)
- Group VIII – monotherapy: Cyproterone (Cypro) hormonotherapy: 3x2tablets/day (50mg/tablet), at 8 hours interval

The hormonotherapy (HT) was an intermittent one and was monitored in the light of prostate specific antigen determination during the whole study.

The liver functionality (hepatotoxicity) was regarded through transaminases activity monitorisation. Determination of transaminases activity (AST and ALT) was performed at well known time intervals: 0 time and after 1, 2, 4, 6 months etc. or at every 3 months if a favorable evolution was recorded, during the whole study, using dry technology on slides (slide provenience: Products Vitros Chemistry). Transaminases activity determinations were assayed at the same time intervals like prostate specific antigen (PSA) determinations and also at one month from the start of the hormonotherapy. For groups IV to VIII (without BO) 0 time is the moment of diagnosis and for the groups I to III 0 time is after the BO procedure.

To ensure that the study would be representative, a differential diagnosis was performed to exclude the presence of viral or alcoholic hepatitis. In addition, in the study there were admitted only the patients with serum transaminases activity levels under 1.5 of the normal value ($< 1.5 \times \text{NV}$).

For each group there were noted the following aspects:

- number of patients with initial value of serum transaminases AST and ALT activity above the normal value;
- number of patients registering during hormonotherapy elevations of serum transaminases activity levels greater than the normal value, but smaller than the double of the normal value (between $1-2 \times \text{NV}$);
- number of patients registering during hormonotherapy elevations of serum transaminases activity levels between $2-4 \times \text{NV}$;
- number of patients registering during hormonotherapy elevations of serum transaminases activity levels four times than the normal value ($4 \times \text{NV}$).

Results and discussion

The hepatotoxicity may be strong, case when the hormonotherapy must be stopped, or not so strong, when hormonotherapy is continued but the patient is strictly medically monitored. If hepatotoxicity is reversible, a new hormonotherapy scheme will be used, but for this study such patients will be „lost from view”.

So, if transaminases activity registered the following increases:

- between $1-2 \times \text{NV}$, hepatotoxicity was not present (Table I). After a certain time interval the values turned onto the normal value (NV)

Table I

The number of patients for which, AST and ALT activity was between 1-2xNV, for the 8 studied groups taken into study

Group	Number of patients
BO+Fluta	5
BO+Bica	-
BO+Cypro	4
Fluta+Gose	4
Leupro	-
Fluta	3
Bica	-
Cypro	4

Bilateral orhiectomy = BO; Flutamide = Fluta; Bicalutamide = Bica;
Cyproterone = Cypro; Goserelin = Gose; Leuprolide = Leupro

The greatest number of patients for which AST, ALT activity values were greater than the normal value, but smaller than the double of the normal value (between 1-2xNV) were registered in the studied group I (BO+Fluta).

- AST and ALT activity values between 2-4xNV: hepatotoxicity was present, but it's considered reversible, not imposing the interruption of the hormonotherapy (Table II).

Table II

The number of patients for which transaminases activity ranged between 2-4xNV and also when AST, ALT activities were greater than four times the normal value (> 4xNV), for the 8 groups taken into study

Group	Number of patients AST and ALT activity values between 2-4xNV	Number of patients AST, ALT activities > 4xNV
BO+Fluta	5	3
BO+Bica	2	-
BO+Cypro	2	2
Fluta+Gose	5	3
Leupro	-	-
Fluta	4	2
Bica	1	-
Cypro	2	2

The greatest number of patients for which AST, ALT activity values were both between 2-4xNV belong to the studied groups I (BO+Fluta) and IV (Fluta+Gose). So, Fluta is the most incriminated in the appearance of reversible hepatotoxicity, the incidence being higher in the case of combined therapy (BO+Fluta and Fluta+Gose) than in monotherapy (Fluta).

●AST, ALT activity values greater than four times the normal value ($> 4 \times \text{NV}$): severe hepatotoxicity was present, which imposed the immediate interruption of the hormonotherapy (Table II).

It was found that Fluta is also the most incriminated in the development of the severe hepatotoxicity, the incidence being higher in the case of combined therapy than in the case of monotherapy. Cypro was also incriminated in the appearance of severe hepatotoxicity which determined the HT stopping. The same incidence was registered for both combined therapy and monotherapy.

An individual variable was registered for the month in which the serum transaminases activity values start to elevate, for the month at which their values reached again the normal values and for the month in which the hormonotherapy was stopped due to severe hepatotoxicity. The time interval during which the transaminases activity levels were elevated was also variable.

From the point of view of the serum transaminases activity values, the highest values were registered in the case of the two combined therapies with Flutamide, approximately equal to each other.

In the case of Flutamide monotherapy, the decreasing order registered for the serum transaminases activity was the following:

$\text{BO} + \text{Fluta} \approx \text{Fluta} + \text{Gose} > \text{Fluta} > \text{BO} + \text{Cypro} > \text{Cypro} > \text{BO} + \text{Bica} > \text{Bica} \geq \text{Leupro}$

In this regard we may conclude that Flutamide was the most hepatotoxic, followed by Cyproterone.

The patients with reversible and severe hepatotoxicity presented a great interest. The greatest number of patients that presented reversible or severe hepatotoxicity was equally distributed in the studied groups I (BO+Flutamide) and IV (Flutamide+Goserelin).

From the total number of patients taken into study (280/8 groups), there were registered 12 cases of severe hepatotoxicity which imposed HT stopping.

For the patients reported with severe hepatotoxicity that imposed the stopping of hormonotherapy, the transaminases activity levels evolution was still registered after the interruption of hormonotherapy, because it was necessary to establish if hepatotoxicity was reversible or not. For this purpose the serum transaminases activity were determined at a week after the HT stopping and then every two weeks until the 17th week. During this time a part of the patients deceased because of extremely severe hepatotoxicity (Table III). For those with a favorable evolution the values became normal.

Table III

The total number of patients deceased during the study, for all the 8 studied groups

Group	Number of patients
BO+Fluta	2
BO+Bica	-
BO+Cypro	1
Fluta+Gose	1
Leupro	-
Fluta	2
Bica	-
Cypro	2

Eight deceases were registered due to severe hepatotoxicity, so only 4 patients had a favorable evolution after HT stopping, patients whose hepatic parameters had normalised in time.

Conclusions

The most incriminated in generating reversible and severe hepatotoxicity is the combined therapy with Flutamide. In these cases the incidence is more elevated than in Flutamide monotherapy. Cyproterone is also incriminated in unleashing reversible and severe hepatotoxicity. In the case of Cyproterone, the incidence of generating hepatotoxicity is the same for combined hormonotherapy and for monotherapy. In conclusion, Flutamide is more hepatotoxic than Cyproterone. A high percentage of deaths were registered due to severe hepatotoxicity.

Therefore, in clinical practice it should be recommended the use of Bicalutamide or Leuprolide in order to avoid hepatotoxicity.

References

1. Kaisary A.V., Murphy G.P., Denis L., Griffiths K., Textbook of prostate cancer, Ed. Martin Dunitz, London, 1998, 303
2. Farcas A., Macavei C., Bojita M., Physicians's attitude towards voluntary reporting of adverse drug reactions, *Farmacia*, 2008, LVI, 5, 563-570
3. McLeod D.G., Tolerability of nonsteroidal antiandrogens in the treatment of advanced prostate cancer, *Oncologist*, 1997, 2, 18-27
4. Klotz L., Schellhammer P., Carroll K., A re-assessment of the role of combined androgen blockade for advanced prostate cancer, *BJU International*, 2004, 93, 1177-1182
5. Cetin M., Demirci D., Unal A., Altinbas M., Guven M., Unluhizarci K., Frequency of flutamide induced hepatotoxicity in patients with prostate carcinoma, *Hum Exp Toxicol*, 1999, 18(3), 137-140
6. Schellhammer P.F., An evaluation of bicalutamide in the treatment of prostate cancer, *Expert Opin Pharmacother*, 2002, 3, 1313-28

7. Kirby R.S., Christmas T.J., Brawer M.K., Prostate Cancer, Ed. Mosby, London, 2001, 178
8. Pinganaud G., Chaslerie A., Bourdel Marchasson I., Decamps A., Manciet G., Emerian J.P., Cyproterone induced hepatotoxicity, *Ann Pharmacother*, 1995, 29(6), 634
9. Murphy B.J., Collins B.J., Severe hepatitis and liver failure induced by Cyproterone acetate, *Aust NZ J Med*, 1996, 26(5), 724
10. Dănciulescu Miulescu R., Mușat M., Neamțu C. The impact of short and medium-term glucocoid treatment on glucose homeostasis, *Farmacia*, 2009, LVII, 1, 17-23
11. Mosula L., Zimenkovsky B., Havrylyuk D., Missir A., Chiriță I., Lesyk R. Synthesis and antitumor activity of novel 2-thioxo-4-thiazolidinones with benzothiazole moieties. *Farmacia*, 2009, LVII, 3, 321-330.

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