Antiandrogen-associated Hepatotoxicity in the Management of Advanced Prostate Cancer

**Background.** Antiandrogens available for patients with advanced prostate cancer are reported to cause hepatotoxicity. The aim of this study is to investigate the antiandrogen-associated hepatotoxicity in patients with advanced prostate cancer.

**Methods.** By retrospective chart review, 229 patients (47–89 years old) with advanced prostate cancer treated by total androgen blockade (TAB) with bilateral orchiectomy or LHRH (luteinizing hormone-releasing hormone) analogues plus antiandrogen, or antiandrogen-radiotherapy were enrolled in this study. There were 124 patients taking flutamide 750 mg daily and 105 patients taking cyproterone acetate (CPA) 150 mg daily. Hepatotoxicity defined by the International Consensus Meeting in 1990 and Food and Drug Administration, USA was used to evaluate the hepatotoxicity (including serious hepatotoxicity).

**Results.** There was a higher occurrence of hepatotoxicity in patients taking flutamide (15.3%) than taking CPA (9.5%) \(p = 0.034\). The occurrence of serious hepatotoxicity of flutamide and CPA was 4.8% (6/124) and 3.8% (4/105), respectively. The mean latency period of hepatotoxicity for CPA was 4.8 ± 2.0 months for flutamide and 5.8 ± 1.9 months for CPA, respectively. The two groups made no significant difference in liver enzyme (mean maximal alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) = 284.2 ± 99.3/300.6 ± 58.5 U/L versus 341.8 ± 67.1/301.6 ± 80.5 U/L). All of the 19 patients (100%) and 9 of 10 patients (90%) with flutamide and CPA-induced hepatotoxicity got self-resolution after discontinuation of the antiandrogens. The average time of self-resolution is 4.5 ± 3.1 months and 6.3 ± 4.7 months for flutamide and CPA, respectively. Five patients of flutamide-induced and 2 patients of CPA-induced hepatotoxicity got resolution after changing to other antiandrogens.

**Conclusions.** Flutamide and CPA appear to cause hepatotoxic effects in some patients. Discontinuation of the antiandrogens seems to be the resolution of hepatotoxicity. A change to other antiandrogens may be an alternative strategy to the antiandrogen-induced hepatotoxicity. The results of this study suggest that all patients receiving flutamide and CPA should be monitored carefully for signs and symptoms referable to hepatic injury to prevent the development of serious hepatic dysfunction.
1989, is also used after orchiectomy or in combination with various luteinizing hormone-releasing hormone (LHRH) agonists. Nevertheless, hepatotoxicity from mild liver function deterioration, hepatitis, fulminant hepatitis and even mortality due to liver failure have been reported in western countries. The occurrence of hepatotoxicity reported ranged from 1 to 5%. Gomez et al. have reported an occurrence of hepatotoxicity in 0.36% of 1,091 consecutively patients treated with prostate cancer (as defined by an increase in serum transaminase activity 4 folds or more above the upper normal limit).

Cyproterone acetate (CPA) is a widely used drug in the treatment of advanced prostatic carcinoma. It exerts a direct antiandrogenic effect on the tumor cells and its metastases, and has an additional negative feedback effect on the hypothalamic receptor, thus leading to reduced gonadotropic release and diminished testicular androgen production. The incidence of CPA-induced hepatotoxicity was noted as 4.5% in the European organization for research and treatment of cancer (EORTC) study.

The number of patients with prostate cancer increased dramatically in recent few years in our country. Antiandrogens were also used frequently in patients with locally advanced or metastatic prostate cancer. The purpose of this study is to investigate the hepatotoxicity induced by flutamide and CPA.

**METHODS**

From January 1994 to June 2000, a total of 229 consecutive patients with advanced prostate carcinoma (stage C or D) were treated with flutamide 750 mg or CPA 150 mg daily in combination with LHRH agonist, orchiectomy or radiotherapy. The patients treated with antiandrogen alone (monotherapy) were also included. Excluded were the patients with history of hepatitis, gall stone, fatty liver, liver cirrhosis, habits of alcohol consumption, and medication that may cause liver injury. Serum alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) were checked before treatment, and then monthly for 3 months and every 3-6 months thereafter. Some patients also had serum alkaline phosphatase (Alk. P), glutamyl transpeptidase (GGT) and total bilirubin (TB) evaluated before and after antiandrogen treatment. The patients’ characteristics are shown in Table 1.

Hepatotoxicity was defined as: mild-to-moderate (liver enzymes elevation 2-6 folds of upper normal limit) and serious hepatotoxicity (liver enzymes elevation greater than 6 folds of upper normal limit). Drug-induced liver injury was defined utilizing the criteria reported by the International Consensus Meeting in 1990. The signs and symptoms of liver disease are generally non-specific. The term “liver injury” is more preferred than hepatitis, necrosis or cholestasis in the description of drug-induced liver disease. The consensus meeting defined liver injury as an increase of more than twice the upper limit of the normal range of ALT or conjugated bilirubin, or a combined increase in AST, Alk. P and TB, proving any one of them is more than twice normal.

The diagnosis of chemically induced liver injury depends on 2 factors: (1) the appropriate clinical setting and (2) the exclusion of the other causes of the liver disease. Support for the diagnosis can be obtained from the clinical response to discontinuation or re-administration of the drug.

Pearson Chi-Square test was used to compare the difference of hepatotoxicity between flutamide and CPA. Independent t-test was used to compare the difference of

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<th>Table 1. Characteristics of patients</th>
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<td>Age (yrs)</td>
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<td>Pre-treatment mean ALT/AST (U/L)</td>
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CPA = cyproterone acetate; Age data expressed as mean ± SD (range).

*p = 0.352, comparison between flutamide and CPA group; *p = 0.227, comparison between flutamide and CPA group.
RESULTS

Occurrence of hepatotoxicity of flutamide and CPA was 15.3% (19/124) and 9.5% (10/105), respectively \((p = 0.034)\). The mean maximal ALT and AST are showed in Table 2. The occurrence of CPA-induced hepatotoxicity is significantly lower than that of flutamide. In CPA group, the levels of serum ALT/AST/Alk. P/GGT/TB were checked in 3 of 10 patients with hepatotoxicity; including 1 with mild-to-moderate hepatotoxicity and 2 with severe hepatotoxicity. The records were 78 U/L/21 U/L/0.3 mg/dL, 244 U/L/193 U/L/21 U/L/0.5 mg/dL, and 1132 U/L/992 U/L/210 U/L/127 U/L/7.6 mg/dL in 3 patients, respectively. In flutamide group, Alk. P, GGT and TB were checked in 4 of 19 patients with hepatotoxicity when it occurred; one was with mild-to-moderate hepatotoxicity and 3 were with severe hepatotoxicity. The ALT/AST/Alk. P/GGT/TB were recorded as 103 U/L/111 U/L/78 U/L/19 U/L/0.8 mg/dL, 382 U/L/313 U/L/29 U/L/22 U/L/0.2 mg/dL, 1035 U/L/745 U/L/145 U/L/140 U/L/7.0 mg/dL, and 216 U/L/201 U/L/92 U/L/77 U/L/0.7 mg/dL in them, respectively. The results of this study implied that the Alk. P, GGT and TB may be abnormal in patients with severe hepatotoxicity.

The latency period of hepatotoxicity and resolution duration after discontinuation of antiandrogen are showed in Table 3. Neither of them showed significant difference between flutamide and CPA.

The distribution of non-hepatotoxic and hepatotoxic group in patients taking antiandrogen is showed in Fig. 1 (flutamide) and Fig. 2 (CPA).

Table 2. Incidence of hepatotoxicity

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<th>Flutamide</th>
<th>CPA</th>
<th>(p) value</th>
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<tr>
<td>Mean [max. ALT/AST (U/L)]</td>
<td>284.2 ± 99.3/300.6 ± 58.5</td>
<td>341.8 ± 67.1/301.6 ± 80.5</td>
<td>0.744(^a)</td>
</tr>
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<td>Incidence of hepatotoxicity</td>
<td>15.3% (19/124)</td>
<td>9.5% (10/105)</td>
<td>0.034(^b)</td>
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Mean [max ALT/AST U/L] = mean ± SD of maximal alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST); CPA = cyproterone acetate; \(^a\)Pearson Chi-Square test

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Table 3. Latency period and resolution duration after discontinuation

<table>
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<tr>
<th></th>
<th>Flutamide</th>
<th>CPA</th>
<th>(p) value</th>
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<tbody>
<tr>
<td>Treatment time (months)</td>
<td>2 - 68</td>
<td>2 - 43</td>
<td>0.841(^a)</td>
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<tr>
<td>Latency period (months)</td>
<td>4.8 ± 2.0</td>
<td>5.8 ± 1.9</td>
<td>0.862(^b)</td>
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<tr>
<td>Resolution duration (months)</td>
<td>4.5 ± 3.1</td>
<td>6.3 ± 4.7</td>
<td>0.622(^c)</td>
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CPA = cyproterone acetate; \(^a\)Independent \(t\)-test.

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Four of the 6 patients with flutamide-induced severe hepatotoxicity were originally treated in combination with orchietomy. An other one had flutamide and radiotherapy. The other 1 was treated with LHRH agonist and flutamide. One patient (radiotherapy and flutamide) was lost to follow-up. Five of them resolved after discontinuation of the antiandrogen for 7.9 ± 4.1 months. Three of the 5 patients changed to diethylstilbestrol, and the other 2 took CPA after the liver function was covered. All the 5 patients had loss of libido and potency after the alternative native treatment. None of them had further liver function deterioration during the follow-up period.

Nine of the 13 patients with flutamide-induced mild-to-moderate hepatotoxicity were originally treated with orchietomy and flutamide; another 2 with radiotherapy and flutamide; and the other 2 with LHRH agonist and flutamide. All of them had resolved liver function after discontinuation of antiandrogen. In the follow-up period, five of them (38.4%) had their dose tapered; 3 changed to CPA, and 2 discontinued antiandrogen. The remaining 3 patients changed to diethylstilbestrol, and 2 of them subsequently changed to bicalutamide due to the side effects of diethylstilbestrol. These patients showed no recurrence of hepatotoxicity in the follow-up period.

A case of pathologically proved flutamide-induced severe hepatotoxicity was included.

In 4 patients with CPA-induced severe hepatotoxicity, 3 were originally treated with orchietomy and CPA, and 1 was treated with LHRH and CPA. All of them got re-
covered from that hepatotoxicity in a mean of 6.9 months after discontinuation of the CPA. Two of the 4 patients no longer required antiandrogen; 1 changed to diethylstilbestrol and the other one switched to bicalutamide. In the following days, no other episode of drug-induced hepatotoxicity was found to occur in them.

In the 6 patients with CPA-induced mild-to-moderate hepatotoxicity, 3 were originally treated with orchietomy and CPA, 2 received radiotherapy and CPA, and 1 received LHRH agonist and CPA. No hepatotoxicity was found to occur in these 6 patients in the follow-up period.

There was no correlation between the duration of antiandrogen treatment (flutamide or CPA) and the elevation of liver enzyme. There was no significant difference in age between the groups of patients with flutamide- and CPA-induced hepatotoxicity. Also, there was no sig-

*including 1 patient had liver enzyme returned to normal after antiandrogen discontinuation at other hospital

Fig. 1. Distribution of non-hepatotoxic and hepatotoxic group in detail of flutamide; mean [max ALT/AST]: mean ± SD value of maximal ALT and maximal AST; ALT or AST > Normal value × 6: ALT or AST greater than six times of the upper limit of normal; S/S + (ALT/AST > Normal value × 2): symptoms or signs of liver function deterioration with ALT or AST greater than two times of the upper limit of normal.

Fig. 2. Distribution of non-hepatotoxic and hepatotoxic group in detail of CPA; mean [max ALT/AST]: mean ± SD value of maximal ALT and maximal AST; ALT or AST > Normal value × 6: ALT or AST greater than six times of the upper limit of normal; S/S + (ALT/AST > Normal value × 2): symptoms or signs of liver function deterioration with ALT or AST greater than two times of the upper limit of normal.
nificant difference of age in hepatotoxic and non-hepatotoxic groups of patients having either flutamide or CPA.

**DISCUSSION**

Both flutamide and CPA play a certain role in the management of advanced prostate cancer, and hepatotoxicity occurs in both of them.

Flutamide and CPA may cause liver injury from mild liver function deterioration, hepatitis with cholestatic or hepatocellular injury, to fulminant hepatitis and even mortality.\(^6,17-19\) Because the possibility of dose-related hepatotoxicity in both flutamide and CPA,\(^20\) early tapering of the dose or discontinuation of the antiandrogen may be a good solution to prevent serious hepatotoxicity.

The occurrence of hepatotoxicity, defined as an elevation of serum aminotransaminase concentration 4 folds or more above the upper normal limit, was 0.36% in 1,091 consecutive prostate cancer patients treated with flutamide.\(^10\) Using this definition, the occurrence of hepatotoxicity in this study was 5.6% and 5.7% for flutamide and CPA, respectively. How ever, the patients with liver enzyme elevation less than 4 folds would be missed. In the EORTC protocol 30892 study, the occurrence of hepatotoxicity is 10.0% and 4.5% for flutamide and CPA, respectively.\(^11\) Lundgren reported one of 10 patients (10%) who had liver injury associated with flutamide.\(^16\) Lund et al. reported the reversal of severe hepatotoxicity after discontinuation of flutamide use in 1 of 20 patients.\(^17\) Consequently, the definition of hepatotoxicity would affect the evaluation of incidence and the results of management.

Liver function deterioration with biochemical abnormality would be necessary to confirm the diagnosis. All clinical and biological manifestations of hepatotoxicity caused by flutamide or CPA progressively disappeared upon discontinuation. It seems to be reversible. Flutamide seems to have more chance to cause hepatotoxicity than CPA. According to our data, in consideration of maximal antiandrogen blockade, the side effect of antiandrogen can be solved by switching flutamide to CPA or vice versa. No hepatotoxicity occurred with the alternative exchange in the sub group with mild-to-moderate hepatotoxicity.

As showed in our data, tapering the dose of flutamide or CPA could resolve the hepatotoxicity. Dose-related hepatotoxicity may be possible in flutamide and CPA. It has also been reported in the long-term use of CPA.\(^20\) To prevent the development of serious hepatic dysfunction, all patients treated with flutamide or CPA should be monitored clinically for signs and symptoms referable to hepatic injury.

ALT and AST could provide 100% sensitivity and specificity of hepatotoxicity as shown in our data. This is also described in the study of Gomez et al.\(^10\)

The mechanism of hepatotoxicity caused by flutamide and CPA is still not fully understood. Flutamide-induced hepatitis is cholestatic and/or cytolytic, and fulminant hepatitis is possible.\(^19\) Fau et al. reported that flutamide is toxic to the rat hepatocytes as a result of the cytochrome P-450 (3A and also 1A)-mediated formation of electrophilic metabolites, whose damaging effects are further aggravated by the inhibitory effect of flutamide on mitochondrial respiration and adenosine triphosphate (ATP) formation.\(^19\) CPA-induced hepatic dysfunction is due to direct or reactive metabolic toxicity.\(^15\)

Our laboratory data showed that antiandrogen-associated hepatotoxicity could induce cytolytic and/or cholestatic liver in jury. The results of this study implied that the Alk.P and TB may be abnormal in patients with serious hepatotoxicity. Based on these findings, we may suggest urologists to check Alk.P and TB before and after antiandrogen treatment even though ALT and AST could provide 100% sensitivity and specificity of flutamide-associated hepatotoxicity.\(^10\)

In conclusion, the results of this study suggest that flutamide and CPA appear to cause hepatotoxicity in some patients with advanced prostatic carcinoma. To prevent the toxicity and its progression, careful follow-up of the liver function before and after antiandrogen treatment is highly recommended. Tapering the dose, discontinuation of antiandrogen, or switching to other antiandrogens may resolve the hepatotoxicity.

**REFERENCES**

1. Johnson J.E., Andersson S.O., Beckman K.W., Lingardh G,


