Ketoconazole and Flutamide in the Treatment of Disseminated Intravascular Clotting from Prostate Cancer : A Case Report and Review

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Abstract

Disseminated intravascular clotting (DIC) is a well-recognized complication of malignancy. Prostatic cancer can produce chronic DIC as well as acute severe DIC. Treatment of DIC are general supportive measures including heparin, transfusion of blood, platelets and clotting factors, but the most important aspect is correction of underlying malignant diseases i.e. cancer of the prostate gland.

For metastatic prostatic cancer presenting with an emergency oncologic condition, the treatment of choice is surgical orchiectomy, but surgery may not be possible in the presence of severe DIC. Ketoconazole and Flutamide† are drugs with different mechanisms for hormonal manipulation of this cancer. Due to severe DIC, we combined both drugs trying to put maximum therapeutic effect on this life threatening profound DIC patient.

Key word : Ketoconazole, Flutamide, DIC, Prostate Cancer

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Prostatic cancer is not a common cancer in Thailand. About 50 per cent of prostatic cancer patients come with obvious metastases and survive for only about a-year and a half. Hormonal ablation is the standard first line treatment for metastatic cases.

Disseminated intravascular clotting (DIC) is a well-recognized complication of malignancy.

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† Flutamide = Fugerel

About 13-25 per cent of chronic DIC are from prostatic cancer[1]. However, prostatic cancer can produce chronic DIC as well as acute severe DIC (purpura fulminans). Treatment of DIC are general supportive measures including heparin, transfusion of blood, platelets and clotting factors, but the most important aspect is correction of underlying malignant diseases i.e. cancer of the prostate gland[2].

Treatment of choice for metastatic prostatic cancer presenting with an emergency oncologic condition is surgical orchiectomy, but surgery may not be possible in the presence of severe DIC. Ketoconazole[3,4] and Flutamide are drugs with different mechanisms for hormonal manipulation of this cancer. We combined both drugs trying to put maximum therapeutic effects on this life threatening profound DIC patient.

CASE REPORT

A 62 year-old Thai male patient was sent to hospital because of fainting. He had had dysuria for 6 months, increasing back pain for 3 months, anorexia and had lost 8 kg in 2 months. Two weeks previously, he developed dyspnea on exertion without orthopnea due to anemia. Without any trauma, he had expanding ecchymosis on his back. He had previously been healthy, didn't smoke and drank occasionally. His family had no history of bleeding disorder.

On physical examination, he was hyposthenic, markedly pale, mildly dehydrated with ecchymosis mostly on the left side of his trunk He had no fever, regular pulse rate 110/min., respiratory rate 18/min., blood pressure 90/60 Torr., good consciousness, and no neurological deficit. A 3x3 cm. hard, fixed, non-tender left supraclavicular lymph node was found. His urinary bladder was full. His prostate gland was enlarged (3 finger breadth), with nodular surface and hard consistency. He didn't have melena, jaundice or sign of chronic liver disease.

Laboratory studies revealed : hemoglobin (Hb) 5.4 g/dl (12-18), platelets 186,000 mm^3 (130,000-400,000) and white blood cells 6,690/mm^3 (4,800-11,000), red blood cells had some macrocyte (1+). Prothrombin time (PT) 20.7 sec. (14.7±0.77), partial thromboplastin time (PTT) 33.5 sec. (37.9±2.21). Serum sodium 117 mmol/l (140-150), potassium 5.3 mmol/l (3.0-5.0), chloride 84 mmol/l (110-115), HCO^{3-} 26 mmol/l (21-34), and normal creatinine. Plain film showed collapsed first lumbar spine.

Hypovolemia and hyponatremia improved with treatment. Even after being treated with vitamin K injections, 5 units of packed red blood cells (PRC), 600 ml of fresh frozen plasma (FFP) and cryoprecipitate transfusion, the ecchymosis progressed extensively. Hemoglobin dropped to 3.8 g/dl and platelets dropped to 34,000/mm^3. DIC profiles showed D-dimer >3,200 mcg./L (<200), euglobulin lysis time >100 min. (<30), fibrin degradation product(FDP) by ethanol gelatin test positive, ristocetin test 1+, factor-I 73.51 mg%, PT 24.1 sec., PTT 42.0 sec., clotting time 19 sec.

Prostatic specific antigen (PSA) reported back later was 555.8 ng/ml (0-4.6). To treat this hormone dependent prostatic cancer, surgical orchiectomy was planned. However, the surgeon decided to delay surgery until the profound DIC had improved. So, ketoconazole 1200 mg/day and Flutamide 250 mg. tid orally were given, hoping for quick medical castration effect. Fraxiparine was also started. PRC and cryoprecipitate transfusions were given.

On the fourth day after ketoconazole administration, the patient developed hypoglycemia with blood sugar 26 mg/dl and cortisol level of 1.44 µg/dl (7.0-25.0). Intravenous steroid was given with complete recovery of hypoglycemia. He developed hemothorax. The pleural content was unclotted, containing 15 per cent red blood cells. Jaundice was detected with total bilirubin 5.5 mg/dl (0.3-1.2), direct bilirubin 3.7 mg/dl (0-0.5), AST (SGOT) 95U/l (0-37), ALT (SGPT) 25U/l (0-40), alkaline phosphatase 148U/l (39-117), GGT 44U/l (7-50).

On the fifth day, DIC had improved. Laboratory tests showed D-dimer >3200 µg/L, euglobulin lysis time >100 min., FDP by ethanol gelatin test positive, ristocetin test 1+, factor-I 657.95 mg%, PT 18.7 sec., PTT 33.6 sec., clotting time 9 sec., hemoglobin 9.3 g/dl, platelets 160,000/mm^3. Bilateral orchiectomy was done under local anaesthesia. Pathological report revealed mild atrophy of testes with tumor emboli.

After surgery, ketoconazole and fugerel were stopped. However, three days after surgery, jaundice increased. Total bilirubin was 15.7 mg/dL, direct bilirubin 13.3 mg/dL AST 407 U/l, ALT 281 U/l, alkaline phosphatase 242 U/l, GGT 217 U/l. Ultrasonography showed mild hepatomegaly without a space occupying lesion, there was no intrahepatic duct or common bile duct dilatation and no spleno-

megaly. This was thought to be multi-factorial from ketoconazole, flutamide, fosfomycin and also sepsis from skin infection. The abnormalities rapidly improved in five days, with complete normalization of liver function a month thereafter.

Two days after surgery, radiation therapy to the collapsed first lumbar spine was given.

Five weeks after surgery, blood test showed D-dimer 800-1600 μg/L, euglobulin lysis time >100, FDP by ethanol gelatin test negative, ristocetin test negative, factor-I 471.29 mg%, PT 16.0, PTT 28.0, clotting time 15 sec., hematocrit 29.8 per cent, hemoglobin 10.0 g/dl, platelets 295,000/mm^3. PSA went down to 24.5 and normalized 7 weeks later.

The patient lost to follow-up, however, he came back 12 months later with bleeding per gum for one week, extensive ecchymosis, hypotension, drowsiness, coffee ground gastric content, Hb 4.0 g/dl, Hct. 12.4 per cent, platelets 3,000/mm^3, PT 42.10, PTT 29.70 sec., BUN 74 mg/dl, creatinine 4.0 mg/dl. FFP with cryoprecipitate, platelet concentrate, whole blood and PRC, normal saline, and dopamine were given. He died 2 days later despite treatment. Autopsy revealed evidence of hemorrhage in the skin. Prostate gland was enlarged with grayish-white friable foci of poorly differentiated adenocarcinoma (Gleason grade 5). There was lymphadenopathy in the paraaortic, mesentery and mediastinum. Tumor showed extensive angio-lymphatic invasion involving lungs, pleura, diaphragm, liver, spleen, kidneys, adrenal glands, esophagus, gastrointestinal tract, pancreas, thyroid and also massive bone marrow invasion. In the brain, there were diffuse microscopic foci of hemorrhage with tumor cells at the center. All these tumor cells showed immunoreactivity with epithelial markers (AE1/AE3, EMA) and PSA. There was no fibrin thrombi.

REVIEW AND DISCUSSION

Disseminated intravascular coagulation is an acquired disorder that occurs in a wide-variety of clinical conditions. It occurs in sepsis, trauma (serious tissue injury, head injury, fat embolism), cancer (myeloproliferative diseases, CA pancreas, CA prostate), obstetrical complications (amniotic fluid embolism, abruptio placentae), vascular disorders (giant hemangioma [Kasabach-Merritt syndrome], aortic aneurysm), reaction to toxin (snake venom, drugs, amphetamines) and immunologic disorders (severe allergic reaction, hemolytic transfusion reaction and transplant rejection)(5).

DIC is characterized by the widespread activation of coagulation including 3 major pathways. (1) Fibrin is formed. Tissue factor expressed on the surface of activated mononuclear cells and endothelial cells binds and activates the factor VII forming complex. This complex activates factor X directly or indirectly by means of activated factor IX and factor VIII. Activated factor X plus factor V convert prothrombin (factor II) to thrombin (factor IIa). Thrombin then affects change of fibrinogen into fibrin. (2) Impairment of anticoagulation. All three physiologic means were involved including antithrombin-III, protein-C, and tissue factor-pathway inhibitor (TFPI). (3) Suppression of fibrinolysis. The high plasma levels of plasminogen-activator inhibitor type-1 (PAI-1) inhibit plasminogen-activator activity and consequently reduce the rate of formation of plasmin. Plasmin then affects the change of fibrin into fibrin-degradation products (FDPs). The combination of increased formation of fibrin and inadequate removal of fibrin results in disseminated intravascular thrombosis. Formation of intravascular thrombin and fibrin occlude small and midsize vessels which compromise the blood supply to organs, resulting in hemodynamic and metabolic derangement and failure of multiple organs.

At the same time, decline in platelets also occurs together with platelet dysfunction. Patients have a tendency to bleed because of decreased circulating coagulation factors, inhibitory effects of fibrinogen fragments on coagulation proteins, thrombocytopenia and platelets dysfunction. The use and subsequent depletion of platelets and coagulation proteins may induce severe bleeding. Bleeding may be the presenting symptom in patients with DIC, complicating decisions about treatment. Although bleeding is the most common clinical feature, disseminated thrombosis is found in some patients at autopsy.

DIC is a well-recognized complication of malignancy. The mechanism of derangement of the coagulation system in patients with cancer is not clear. However, a number of studies have indicated that the tissue factor which is expressed on the surface of tumor cells is involved(6).

Ten to 15 per cent of patients with metastasized tumors have evidence of DIC. For hematologic malignancy, approximately 15 per cent of acute

leukemia had DIC[7,8]. A distinct form of DIC is frequently encountered in patients with acute promyelocytic leukemia (APL). Treatment with all-trans-retinoic acid, however, has drastically reduced the incidence of severe DIC in patients with APL[9]. For solid tumors, DIC is found more common in pancreatic cancer and prostatic cancer than in other cancers. About 13-25 per cent of chronic DIC are from prostatic cancer[1]. Prostatic cancer can produce chronic DIC as well as acute severe DIC (purpura fulminans).

Prostatic cancer is not a common cancer in Asia. In Thailand, it was not listed in the top ten leading cancers. In 1993, only 832 estimated new cases in Thailand were reported, with an age standardized annual incidence rate(ASR) of 4.4/100,000 population[10]. In 1997, we had only 47 new cases of prostatic cancer in our hospital[11]. Generally, about half of prostatic cancer patients come with obvious metastases and survive only about a year and a half. Hormonal ablation is the standard first line treatment for metastatic cases.

Treatment of severe DIC is not easy. Orchiectomy provides the fastest irreversible castrate level of testosterone within 2-6 hours, but may not be possible in the presence of severe DIC[12]. Usually, heparin is administered primarily to inhibit the formation of microthrombi, even when the dominant clinical feature may be hemorrhage. Bleeding can worsen initially. Therefore, immediately after heparin, bleeding diathesis should be treated by replacing the depleted platelets and clotting factors. Transfusion without prior administration of heparin only enhances thrombosis and does not effectively correct the plasma deficiency state. However, the most important aspects of DIC treatment are correction of underlying diseases and general support measures[2].

Ketoconazole has been accepted as a form of hormonal manipulation in prostatic cancer[3,4]. DIC treated with ketoconazole has been reported [13,14]. It is indicated for initial empiric therapy when orchiectomy is contraindicated. Bleeding from DIC can be controlled within 48 hours and subsequently correct coagulopathy[15]. Ketoconazole has significant activity even in those whose disease progressed after flutamide[16]. It has a strong inhibitory effect on testosterone synthesis. At a high dose (400 mg orally, three times daily), it inhibits both gonadal and adrenal steroidogenesis by disrupting the P450-dependent enzyme system, causing rapid decrease (90%) of testosterone and adrenal androgen precursor (70%). Corticosteroid replacement may be needed[17-20].

Serum testosterone level goes down below 20 per cent to 35 per cent of baseline level within 24 hours with mean initial half life of 0.72-1.38 hours and near castrate level in 48 hours[21]. However, increase in testosterone level of 11.5-17.7 per cent over baseline can happen with ketoconazole treatment[22]. After castration by surgery or chemically, however, serum testosterone level only fall by 90-95 per cent and the decrease in intraprostatic level of dihydrotestosterone (DHT) is only around 50-60 per cent. Adrenal androgen precursors (i.e. androstenedione and dihydroepiandrosterone) which are converted to the active androgen DHT, can be partially neutralized by antiandrogen which compete with DHT for binding to the androgen receptor.

Flutamide competes with DHT receptors and exerts its antitumor effects by suppressing nuclear androgen binding. It is a potent non-steroidal antiandrogen. Flutamide does not suppress gonadotropin and testosterone but during the initial weeks of treatment elevation (but still within normal range) of testosterone and (to a lesser degree) leutenizing hormone does occur. These hormone changes usually stabilize with time and return to mean levels after several weeks. There is probably no clinical significance to the initial rise in testosterone level. Flutamide as mono-therapy has shown significant activity in previously untreated prostatic cancer[17]. However, in some studies, it is inferior to orchiectomy when PSA level is above 120 ng/ml[23].

Flutamide is well tolerated. Its side effects include diarrhea (10-15%), abdominal cramps, and abdominal gas pain. Cholestatic hepatitis, likely idiosyncratic, has been reported following the use of flutamide[24]. Ketoconazole 400 mg po tid is extremely well tolerated[16]. Ketoconazole may cause abnormal liver enzymes without significant liver biopsy changes. About 50 per cent of patient may have mild elevated transaminases that resolves with drug cessation. Several series did not find this to be a significant problem,[25-27] however, idiosyncratic fatal massive hepatic necrosis can happen [28]. Flutamide as well as ketoconazole has been used together with other drugs: i.e. luteinizing hormone-releasing hormone analogues.

Complete androgen blockade using Leuprolide (gonadotropin releasing hormone, GNRH analogue) together with Flutamide in US Intergroup study was shown to be superior to single treatment, (29) though some controversy persists. However, leuprolide takes 14 days to achieve castrate level of testosterone(30).

The combination of both ketoconazole and Flutamide may possibly quickly lower testosterone to near castrate level without surgery and at the same time blocking those residual androgen receptors. This combination, theoretically, should be useful in an emergency situation such as profound DIC. In the presented patient, however, it took 5 days for DIC to be under control before the surgeon could do the orchiectomy. Hepato-toxicity did occur, although it was thought to be multi-factorial. Further evaluation of this combination in DIC should be done with caution.

SUMMARY

Due to severe DIC, we gave both ketoconazole and flutamide together in this advanced prostate cancer patient trying to maximize androgen blockade. Even with only a short course (5 days) of treatment, however, hepatotoxicity developed. Combination of both drugs did not result in better control of DIC (it took 5 days to be considered safe for surgery) and may have caused more liver damage in the presence of other hepatotoxic drug or sepsis. We did not give steroid together with ketoconazole in this case due to existing infection and hypoadrenal did developed. Giving corticosteroid together with high dose ketoconazole should be a safer policy whenever there is no contraindication.

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การรักษาภาวะลิ่มเลือดอุดตันกระจายทั่วไปในหลอดเลือดจากมะเร็งของต่อมลูกหมากด้วยยาคีโตโคนาโซล ร่วมกับยาฟลูตาไมด์ : รายงานผู้ป่วยและทบทวนรายงาน

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ภาวะลิ่มเลือดอุดตันกระจายทั่วไปในหลอดเลือดเกิดได้ในมะเร็งหลายชนิด สิบสามถึงยี่สิบห้าเปอร์เซ็นต์ของภาวะลิ่มเลือดอุดตันกระจายทั่วไปในหลอดเลือดชนิดเรื้อรังเกิดจากมะเร็งของต่อมลูกหมาก มะเร็งของต่อมลูกหมากยังอาจทำให้เกิดภาวะลิ่มเลือดอุดตันกระจายทั่วไปในหลอดเลือดชนิดเฉียบพลันได้ด้วย ผู้ป่วยมักมาด้วยภาวะเลือดออก นอกเหนือจากการรักษาโดยการให้ยากันการแข็งตัวของเลือด, ให้สารช่วยการแข็งตัวของเลือด, เกล็ดเลือด และรักษาประคับประคองทั่วไปแล้ว การรักษาที่สำคัญที่สุดคือรักษาที่ตัวมะเร็งเอง ซึ่งในโรคมะเร็งของต่อมลูกหมากระยะแพร่กระจายนั้น การรักษาหลักคือการตัดอัณฑะออกทั้งสองข้างเพื่อกำจัดแหล่งผลิตฮอร์โมนเพศชายออกไป ซึ่งในกรณีที่มีภาวะลิ่มเลือดอุดตันกระจายทั่วไปในหลอดเลือดและภาวะเลือดออกง่ายหยุดยากนั้น อาจไม่สามารถทำการผ่าตัดได้

ยาคีโตโคนาโซลช่วยลดระดับของเทสโทสเตอโรนลงได้อย่างรวดเร็วแต่ไม่สมบูรณ์ เราจึงใช้ยานี้ร่วมกับยาฟลูตาไมด์ ซึ่งออกฤทธิ์ต้านเทสโทสเตอโรน (แต่ไม่ช่วยลดระดับของเทสโทสเตอโรน) ในผู้ป่วยหนึ่งรายที่มาด้วยภาวะเลือดออกรุนแรงจากโรคมะเร็งของต่อมลูกหมากระยะแพร่กระจาย รายงานนี้มีรายละเอียดของผู้ป่วยดังกล่าวรวมถึงผลการรักษาและสรุปรวบรวมรายงานเกี่ยวกับภาวะนี้รวมถึงยาคีโตโคนาโซลและยาฟลูตาไมด์

คำสำคัญ : คีโตโคนาโซล, ฟลูตาไมด์, DIC, มะเร็งต่อมลูกหมาก

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