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Successful use of docetaxel for emergency treatment of disseminated intravascular coagulation due to hormone-refractory metastatic prostate cancer

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ABSTRACT

Disseminated intravascular coagulation (DIC) is a fatal presentation of metastatic adenocarcinoma of the prostate. A 59-year old male presented with a 2-week history of fatigue, red urine, and bruises on his body. Physical examination and ultrasonography showed that the patient had an enlarged prostate. Laboratory analysis was consistent with DIC. The patient's PSA level was 90 ng mL^{-1}. Bone scintigraphy showed diffuse metastasis. Histopathological analysis of a biopsy specimen showed prostate adenocarcinoma. Acute DIC improved rapidly following initiation of leuprolide and bicalutamide hormone therapy. The patient's PSA dropped from 90 to 0.01 ng mL^{-1} after 1 month of treatment. The patient had recurrence of the initial complaints and elevated PSA while receiving leuprolide treatment in first year. As the patient's clinical condition deteriorated, we initiated docetaxel-containing chemotherapy. The patient's symptoms became less severe and his abnormal laboratory findings began to normalize after 2 weeks of the chemotherapy, and they completely resolved returned to normal after 2 months. In conclusion, docetaxel-containing chemotherapy in a patient with metastatic prostatic carcinoma and DIC was effective, despite a low platelet count and bleeding.

1. Introduction

Acute overt disseminated intravascular coagulation (DIC) in cancer patients is rare and often fatal. Although laboratory evidence of abnormal coagulation is common, clinically evident bleeding is rare in patients with solid tumors. The incidence of DIC in cancer patients is difficult to estimate, as it is associated with many different cancers and related conditions. Malignant disease may be complicated by DIC in 7%–20% of cases.[1] Unknown primary cancers, and cancers originating in the lungs, breast, and prostate were responsible for almost 50% of cases with DIC, the majority of which were adenocarcinomas. DIC, with or without overt bleeding, can be a presenting sign of prostate cancer. Agents used to treat DIC in prostatic cancer patients include ketoconazole, samarium, strontium, and estrogens. There is limited experience with chemotherapy in this setting. Herein we report the successful treatment of a patient with DIC due to metastatic prostate carcinoma using leuprolide and bicalutamide, followed by docetaxel-containing chemotherapy.

2. Case report

A 59-year-old male presented to hospital with a 2-week history of fatigue, red urine, and bruises on his body. The patient's medical history was non-contributory. The patient had a reduced performance status, but was hemodynamically stable. Physical examination showed widespread ecchymosis, and an enlarged prostate gland that was hard and nodular. There were no other physical abnormalities.

The patient had a hemoglobin level of 9.3 g dL^{-1} (normal range: 11–17 gdL^{-1}), leukocyte count of 3400 μL^{-1} (normal range: 4.1–11 μL^{-1}), and platelet count of 27 mL^{-1} (normal range: 150-450 mL^{-1}). The prothrombin time (PT) and activated partial thromboplastin time (aPTT) were 19.9 s (normal range: 10–14 s) and 36.5 s (normal range: 19–32 s), respectively. The patient's fibrinogen and d-dimer

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levels were 108 mg dL^{-1} (normal range: 200–400 mg dL^{-1}) and 4.4 mg L^{-1} (normal range: 0–0.55 mg L^{-1}), respectively. The following serum levels (normal values for our laboratory in parentheses) were as follows: total bilirubin: 1.24 (0–1.3) mg dL^{-1}; indirect bilirubin: 0.86 (0–0.8) mg dL^{-1}; alkaline phosphatase: 953 (40–129) U L^{-1}; gamma glutamyl transferase: 45 U L^{-1} (5–61); lactate dehydrogenase: 730 (240–480) U L^{-1}; alanine aminotransferase: 22 (0–41) U L^{-1}; aspartate aminotransferase: 53 (0–38) U L^{-1}; creatinine: 0.44 (0.5–1.2) mg dL^{-1}. Prostate-specific antigen (PSA) was 90 ng mL^{-1} (normal range: 0–4 ng mL^{-1}). Abdominal ultrasound showed that the liver, spleen, and kidneys were normal, but that the prostate gland was enlarged and heterogenic. Examination of a blood smear was consistent with normochromic/normocytic anemia, fragmented erythrocytes, and low number of platelets and large platelets.

The patient was diagnosed as DIC and prostate carcinoma was considered the likely cause, as the prostate examination and ultrasonography findings showed that the patient's prostate was enlarged and PSA was high. Histopathological examination of a transrectal ultrasound-guided biopsy specimen of the prostate showed adenocarcinoma; the Gleason score was $4 + 4 = 8$. Whole-body bone scintigraphy showed multiple metastases. The patient was treated with fresh frozen plasma, packed red blood cells, and platelets, but hematuria, ecchymosis, and other complaints persisted. The patient was treated with leuprolide acetate 11.25 mg every 3 months and bicalutamide 50 mg d^{-1}. Leuprolide acetate was continued indefinitely and bicalutamide was withdrawn after 2 months. All the patient's clinical and laboratory findings returned to normal 1 month after the treatment was started. After 1 months of the treatment the patient's PSA dropped from 90 to 0.01 ng mL^{-1}. The patient was followed-up bimonthly via clinical examination and PSA measurement.

One year later from the initial diagnosis the patient again presented to our clinic with fatigue, ecchymosis, and hematuria. Laboratory findings were as follows: hemoglobin level: 8 g dL^{-1}; leukocyte count: 3000 μL^{-1}; platelet count: 19 mL^{-1}; PT: 22 s; aPTT: 38 s. Fibrinogen and d-dimer levels were 150 mg dL^{-1} and 6 mg L^{-1}, respectively, and the PSA level was 102 ng mL^{-1}. We considered that the patient was resistant to hormone therapy and initiated chemotherapy consisting of docetaxel 25 mg m^{-2} QWK and prednisolone 4 mg b. i.d. which was supported by fresh frozen plasma, packed red blood cells, and platelets. The patient's complaints became less severe and his abnormal laboratory findings began to normalize 2 weeks after the start of docetaxel therapy, and they completely resolved returned to normal after 2 months. The patient's PSA level dropped from 102 to 0.004 ng mL^{-1}. Chemotherapy was stopped after 6 months. The patient was then followed-up with normal hematologic parameters for >5 months.

3. Discussion

The therapeutic cornerstone of DIC is treatment of the underlying disorder. In fact, if the malignant disease can be brought in remission, the DIC will usually simultaneously disappear.[2]

Supportive therapy may consist of anticoagulant treatment, however, the efficacy and safety of this strategy in cancer patients with DIC has never been studied in sound clinical studies. Based on the notion that DIC is characterized by extensive activation of coagulation, anticoagulant treatment may be a rational approach. There are no clinical randomized controlled trials demonstrating that the use of heparin in patients with DIC results in an improvement of clinically relevant outcomes. Small, uncontrolled studies have shown that (low molecular weight) heparin is capable of improving laboratory abnormalities associated with DIC. Patients with DIC (and in particular those with cancer) are at high risk of venous thromboembolic events (VTEs) due to the cancer itself and additional factors, including advanced age, recent surgery, immobilization, in-dwelling vascular catheters, and previous VTE history. Therefore, VTE prophylaxis using unfractionated heparin (UFH) or low molecular weight heparin (LMWH) has become standard of care in patients with cancer and DIC.

Based on the notion that depression of the protein C system may significantly contribute to the pathophysiology of DIC, supplementation of activated protein C might potentially be of benefit. Indeed, in experimental sepsis studies activated protein C was shown to be effective in reducing mortality and organ failure. The role of restoring defective physiological anticoagulant pathways (e.g. by administration of antithrombin or activated protein C concentrates) in patients with cancer has not been evaluated so far.

Low levels of platelets and coagulation factors may increase the risk of bleeding. However, plasma or platelet substitution therapy should not be instituted on the basis of laboratory results alone, but is only indicated in patients with active bleeding and in those requiring an invasive procedure or otherwise at risk for bleeding complications. The threshold for transfusing platelets depends on the clinical situation of the patient.

In patients with severe bleeding, antifibrinolytic treatment may be considered. In fact, since fibrin deposition, partly due to insufficient fibrinolysis, is an important feature of DIC, further inhibition of the fibrinolytic system seems not appropriate. An exception may be made in those rare cases that primary or secondary hyperfibrinolysis dominates the clinical picture. Uncontrolled observations and one randomized controlled clinical trial have shown the beneficial effect of antifibrinolytic agents in this situation. There are some anecdotal reports of the successful use of recombinant factor VIIa in cancer patients with DIC and life-threatening bleeding but the efficacy and safety of this treatment in DIC is unknown.

DIC is the most common coagulation disorder in patients with prostate cancer, which may occur as a result of the introduction of thromboplastic substances into the blood stream following biopsy of either the primary tumor or a metastatic site, or it may develop as a manifestation of advanced disease. Nonetheless, DIC as a primary manifestation of prostate cancer is unusual.[3] The cornerstone of managing DIC is treatment of the underlying disorder. The optimal treatment method for DIC in patients with prostatic carcinoma remains contentious. Frozen fresh plasma, heparin, and platelets are commonly administered for palliation. Various forms of therapy, including high-dose stilbestrol [4], rapid induction of the castrate state using ketoconazole [5], samarium 153 [6], and strontium-89 [7] have also been reported to be effective.

The literature contains a few reports of patients with DIC due to metastatic prostate carcinoma that were successfully treated with chemotherapy. Avances et al.[8] reported a patient that was successfully treated with a chemotherapy regimen that included docetaxel and cisplatin, and Smith [9] reported 2 patients that were successfully treated with mitoxantrone-containing chemotherapy. Albiges et al.[10] reported a 55-year-old patient that had a normal prostate on clinical examination, and thrombocytopenia with incomplete diffuse intravascular coagulopathy. The patient was initially treated with hormone therapy, followed by chemotherapy that included docetaxel. Talebi et al.[11] reported a patient with metastatic castration-resistant prostate cancer and DIC, as well as both clotting and bleeding in addition to thrombocytopenia. The patient (despite a platelet count of 46,000 mm^{-3}) was treated with docetaxel-containing chemotherapy, which resulted in resolution of DIC, normalization of the platelet count, and resolution of hematuria. To the best of our knowledge the present case report is the third to report the successful management of DIC associated with androgen-independent prostate cancer using chemotherapy that included docetaxel and prednisolone.

In conclusion, docetaxel-containing chemotherapy for metastatic prostatic carcinoma-induced DIC may be effective even though patients may have a low platelet count and bleeding. Chemotherapy may be a single treatment modality that improves survival in these patients.

Conflict of interest

None declared.

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