Mitoxantrone-related acute myeloblastic leukaemia in a patient with metastatic hormone-refractory prostate cancer

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Mitoxantrone is a DNA topoisomerase II poison commonly used for the treatment of hormone-refractory prostate cancer. The risk of secondary leukaemia is well described after mitoxantrone treatment in breast cancer and multiple sclerosis. Recent improvements of systemic chemotherapy increased the median survival in patients becoming resistant to androgen deprivation from 10 to 18 months. As a consequence, chemotherapy-related cumulative toxicities may become a more prominent clinical problem in this patient population. We report here the first case report of secondary leukaemia induced by mitoxantrone in metastatic hormone-refractory prostrate cancer. This clinical observation invites us to reconsider the number of administrations to be recommended for mitoxantrone-sensitive metastatic prostate cancer patients. ***Anti-Cancer Drugs*** **18:233–235 © 2007 Lippincott Williams & Wilkins.**

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Introduction

Prostate cancer is the most common type of cancer and the third leading cause of death from cancer in men in the western countries [1]. The mainstay of initial management of metastatic prostate cancer is hormonal castration [2,3]. Until recently, after failure of androgen ablation, few treatment options, however, were available. Systemic chemotherapy may provide clinical response, pain control and improved quality of life [4,5]. Before the introduction of docetaxel, no benefit in overall survival (OS) had been established. In 2004, two phase III clinical trials [6,7] have shown significant improvement of OS in metastatic hormone-refractory prostate cancer (HRPC). In this palliative setting, the median survival is currently around 18 months in patients who received docetaxel [6–8].

Mitoxantrone is a DNA topoisomerase II poison widely used in cancer therapy, especially in prostate cancer patients. A potential complication of DNA-damaging agents is secondary acute leukaemia, which has been related to chemotherapy as observed with alkylating agents such as melphalan [9] or with topoisomerase II poisons such as epipodophyllotoxins, mitoxantrone and anthracyclines [10,11]. Improved median survival of this patient population also increases the risk of delayed complications and rechallenges the benefit/risk ratio of anticancer treatments.

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Case report

A 64-year-old patient with HRPC metastatic to the bone presented to our institution in October 2002. He had no prior radiation therapy.

Over 12 months, he received mitoxantrone as short infusions of 12 mg/m^2 every 21 days. A total of nine administrations were performed, corresponding to a cumulative dose of 108 mg/m^2. The patient presented a clinical and biological prostate-specific antigen (PSA) response under mitoxantrone treatment. The PSA levels fell from 1082 to 8.2 ng/ml. At disease progression, he had asymptomatic PSA increase and received four cycles of docetaxel. Then, he was enrolled in a phase I trial combining irofulven (0.4 mg/kg every 2 weeks) and capecitabine (2000 mg/m^2/day for 2 weeks every 4 weeks) for three cycles.

In October 2003, he developed asthenia, dyspnea and spontaneous epistaxis. Physical examination revealed multiple ecchymosis and purpura. Blood tests showed leucopenia (1200×10^9/l) without blast cells, severe anaemia (Hb = 6.2 g/l) and thrombocytopenia ($18\,000 \times 10^9$/l). Bone marrow aspirate showed an increased cellularity with 26% of blast cells. Morphology, cytochemistry and immunological phenotype analysis of blast cells identified a tumoral proliferation of CD34$^+$, CD13$^+$, CD33$^+$, CD117$^+$, DR$^+$ cells. The diagnosis of type 4

acute myeloblastic leukaemia, according to the French American British classification, was made. The karyotype of leukaemic cells was 46 XY, inv(16) (p13q22).

Fluorescent in-situ hybridization showed a specific rearrangement MYH11/16p13 and inv(16) (p13q22), a typical cytogenetic feature of topoisomerase II poison-related acute myeloblastic leukaemia [12]. Rearrangements of the mixed-lineage leukaemia gene were absent.

The induction chemotherapy consisted of cytarabine (200 mg/m^2/day as continuous intravenous infusion for 7 days) and idarubicine (8 mg/m^2/day for 5 days) according to the Groupe Ouest Est Leucemies Aigues Myeloblastiques trial [13]. The patient achieved a complete remission and later received consolidation chemotherapy. The outcome was favourable with a follow-up of 12 months, but prostate cancer progressed with diffuse bone marrow involvement. The patient died of prostate cancer progression 26 months after the onset of androgen independence and 14 months after the diagnosis of leukaemia.

Discussion

We describe here the first case of secondary leukaemia induced by mitoxantrone in metastatic HRPC. The risk of leukaemia after mitoxantrone treatment in breast cancer and multiple sclerosis is well described [11,14]. Chaplain *et al.* [11] studied the risk of leukaemia after adjuvant chemotherapy for breast cancer in a French cohort of 3000 women between 1982 and 1996. Ten cases of acute leukaemia occurred in the first 4 years of follow-up, whereas, none of them did after this period. The average time between breast cancer and leukaemia diagnosis was 24.2 months (range 10–42 months). The relative rate of leukaemia was 28-fold higher in women receiving a combination of radiotherapy and chemotherapy ($P < 0.0001$) compared with women receiving radiotherapy alone and the general female population.

The 4-year cumulative rate of leukaemia ranged from 0.14% in patients who received radiotherapy only to 1.12% in those who received a combination of radiotherapy and chemotherapy. In addition, the risk of leukaemia gradually increases with cumulative doses of mitoxantrone. The 4-year cumulative rate of leukaemia ranged from 0.63% for a cumulative dose ≤ 56 mg/m^2 to 3.89% for a cumulative dose > 56 mg/m^2. The dose-dependent effect of mitoxantrone strongly suggested a causal relationship.

In our patient, this causal relationship was likely in view of the direct chromosomal damages concerning the topoisomerase II gene, lessening the likelihood of a putative role of other chemotherapeutic agents (docetaxel, irofulven, capecitabine) in leukaemogenesis.

Several studies [15–19] have estimated that the cumulative probability of developing acute leukaemia after autologous stem cell transplantation for lymphoma ranged from 3.8 to 14.2% at 5 years.

The outcome of patients with secondary leukaemia is poor. Neugut *et al.* [20] have evaluated a 1-year OS rate at 10%. Harrison *et al.* [21] have reported actuarial 5-year and 10-year survival rates of 17.4 and 8.7%, respectively. The 2-year OS rate was 8% in a retrospective study of 46 patients with secondary leukaemia [22]. Allogenic stem cell transplantation is frequently offered to patients with secondary leukaemia. Transplantation, however, is offered to a limited subset of patients without altered clinical status and having access to a compatible donor. In this setting, the outcome remains poor with 5-year disease-free survival ranging from 16 to 24.4% [20,21]. Nonetheless, such authors suggest that cytogenetic abnormalities could help to choose the therapeutic strategy: patients with a favourable karyotype [e.g. inv(16), t(8,21)] should be treated as de-novo acute myeloblastic leukaemia cases, whereas, palliative treatment or experimental approaches should be considered for patients with a complex aberrant karyotype [12,23].

Conclusion

Given the increasing incidence of prostate cancer and the recent advances in its treatment, medical oncologists will be facing more long-term surviving patients with metastatic prostate cancer. Thus, we may expect an emerging problem, consisting of the potential delayed side-effects of chemotherapy in this patient population. On the basis of this observation, we recommend to reconsider the number of cycles of mitoxantrone in prostate cancer patients with mitoxantrone-sensitive disease and to pay attention to the cumulative dose. The cumulative dose may be responsible for both increased risk of heart failure and secondary leukaemia.

Moreover, it appears essential to characterize the karyotype of the secondary leukaemia, because some of them may be as chemosensitive as de-novo leukaemia as reported here.

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