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Effects of Antineoplastic Treatment of HIV-positive Patients with Testicular Cancer

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Abstract—*Among* 101 *patients with testicular cancer referred to the Department of Oncology ONB, Finsen Institute, four were proven HIV-positive before admission. Three of these patients were treated with cisplatin, 4-epi-podophyllotoxin (VP-16, Etoposide®) and bleomycin. One patient with stage I of the testicular cancer was observed, after orchiectomy, without medical antineoplastic treatment.*

In the HIV-positive patients treated with cytotoxic drugs, leucopenia was seen after one (8%), *fever after three* (23%) *and thrombocytopenia after two* (15%) *courses. Amongst patients not proven HIV-positive leucopenia, fever and thrombocytopenia were seen after* 11 (9%), 21 (18%) *and* 27 (29%) *courses.*

Two patients had stage II and two patients stage III of the HIV infection prior to treatment. The clinical stage of the disease did not change during the course of chemotherapy.

We suggest that HIV-positive patients (stage II and III) with germ cell tumours should be treated with the same aggressive chemotherapy as given to other patients, not proven HIV-positive.

INTRODUCTION

IN MANY COUNTRIES testicular cancer is the most common cancer in men between 15 and 35 years. In Denmark the incidence of testicular cancer is one of the highest in the world being 16.9 per 100,000 in this age group [1].

Infection with the human immunodeficiency virus (HIV) is primarily observed within the same age group. At present there are 1700 verified cases of HIV-positive patients in Denmark of which 90% are men [2].

Over a period of 20 months, four HIV-positive patients with testicular cancer were referred to the Department of Oncology, Finsen Institute for further treatment.

In HIV-positive patients with symptoms of acquired immunodeficiency syndrome (AIDS), aggressive chemotherapy has been used in the treatment of non-Hodgkin's lymphoma. Likewise other cancers associated with immunodeficiency, i.e. lymphomas, have been treated. In these subgroups, treatment with chemotherapy has been complicated by a high incidence of often fatal opportunistic infections [3–6]. Furthermore, amongst HIV infected patients without fulminant AIDS, methotrexate has been suggested as inducing AIDS [7].

At present there is only one report of testicular cancer in two HIV-positive patients; in one of these patients the immunological parameters were monitored before and after chemotherapy. The levels of T-helper cells and T-suppressor cells were maintained [8]. The patient received cisplatin, vinblastine and bleomycin as introduced by Einhorn and Donohue [9].

The combination of cisplatin, VP-16 and bleomycin, as used nowadays in the treatment of testicular cancer, carries a high degree of curability and should therefore in appropriate dosages be offered to all patients with this disease. It is conceivable that problems can occur when applying this aggressive treatment to immunocompromised patients.

Hence we have found it of interest to report the treatment results of the four cases.

PATIENTS AND METHODS

Between 1 May 1986 and 31 December 1987 101 patients with testicular cancer were referred to the Department of Oncology, Finsen Institute. In all patients orchiectomy was performed and the malignant disease verified and classified histologically. Four of these patients were proven HIV-positive before admission. The remaining 97 patients were not proven HIV-positive and have not

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been tested. The 97 patients represented all stages of the malignant disease. From patients treated using the same drugs and dosage, 30 were picked at random. These were used as a control group.

Patients with stage I disease (limited to testis) were treated with orchiectomy only. Patients with stage II and III were treated with cisplatin 20 mg/m^2 and VP-16 100 mg/m^2 days 1–5, every 3 weeks together with bleomycin 15 mg/m^2 weekly. At least four courses were given. If residual tumour was demonstrated, patients underwent surgery.

The degree of myelosuppression was evaluated by nadir values of white blood count (WBC), platelet count, counting the number of leukopenic episodes with WBC $<1.0 \times 10^9$/l, the number of thrombocytopenic episodes with platelet count $<100 \times 10^9$/l and the number of required transfusions. Transfusions were given if haemoglobin fell below 6.0 mmol/l and/or on symptoms on anaemia. The number of episodes of fever, temperature >38°C for more than 12 h or temperature >38.5°C for more than 2 h, were counted. The microflora revealed was also noted.

The patients were staged regarding the HIV infection according to the CDC classification [10]. The CD4+ value and the CD4/CD8 ratio were evaluated and used to monitor the immunological parameters, in the patients who received chemotherapy. One patient refused to have these values checked.

For statistical evaluations the χ^2 test with Yates correction was used.

Patient No. 1

A 34-year-old homosexual male proven HIV-positive 1 month earlier. Histology: embryonal carcinoma.

The patient was classified as having stage I disease and was controlled monthly without treatment. After 5 months, an increase in human chorionic gonadotrophin (HCGβ) and alpha-fetoprotein (AFP) was observed together with retroperitoneal and bilateral lung metastases. Four courses of chemotherapy were given. Tumour markers normalized after the first course. Secondary surgery after the fourth course was performed and necrotic tissue was found in the retroperitoneum.

At present the patient is alive and without evidence of testicular cancer with an observation time of 19 months.

Patient No. 2

A 33-year-old homosexual male, proven HIV-positive 2 months earlier. Histology: seminoma, stage IIIb.

HCGβ was elevated and four courses of chemotherapy were given. After the first course serum markers normalized. At secondary surgery the residual tumour was found to consist of fibrosis without malignancy.

At present the patient is alive and without evidence of testicular cancer with an observation time of 21 months.

Patient No. 3

A 37-year-old homosexual male, proven HIV-positive 14 months earlier. Histology: immature teratoma, stage IIc.

HCGβ was elevated. After four courses HCGβ had decreased but was still elevated, and the patient was given a fifth course. Secondary surgery was performed and histological examination of the retroperitoneal tumour revealed mature teratoma.

At present the patient is alive and without evidence of testicular cancer with an observation time of 19 months.

Patient No. 4

A 27-year-old homosexual male, proven HIV-positive 12 months earlier. A frozen plasma sample taken from the patient in 1980 was also found seropositive. Histology: seminoma, Stage I.

At present the patient is alive and without evidence of testicular cancer with an observation time of 16 months.

RESULTS

All four patients had normal baseline values of haemoglobin, WBC and platelets.

In the three patients who received aggressive chemotherapy one out of 13 courses (8%) resulted in leucopenia. In the control group 11 episodes were seen after 120 courses (9%). Three episodes of fever were seen in the HIV-positive patients (23%) and 21 episodes in the control group (18%). Two episodes of thrombocytopenia were seen in the HIV-positive group (18%) and 27 (23%) in the control group. These values do not differ statistically. Twenty-four transfusions (21 of these to one patient) were given to the HIV-positive patients and 69 to the patients in the control group.

One HIV-positive patient had septicaemia, the bacteria isolated were *Staphylococcus aureus*, *Klebsiella pneumonia* and *Enterobacter*. Two patients in the control group had septicaemia, the bacteria isolated were *Staphylococcus aureus* and *epidermidis*.

The toxicity of the chemotherapy is summarized in Table 1.

At the time of the diagnosis all four patients had a marked decrease in the CD4/CD8 ratio ('helper to suppressor ratio') and two had pronounced CD4+ lymphocyte depletion suggesting severe immunodeficiency. After chemotherapy the three patients had the same stage of the HIV infection. The level of CD4+ and the CD4+/CD8 ratio, in two patients, had not decreased.

Table 1. Toxicity of chemotherapy given to three HIV-positive men with testicular cancer (nadir values)

Patient No.	White blood count (10^9/l)	Platelets (10^9/l)	Haemoglobin (mmol/l)	Transfusion No.	Infection	Bacteriological agent	Antibiotics
1	2.2	101	5.5	3	None		
2	0.3	41	5.0	21	Septicaemia	*Staphylococcus aureus*, *Klebsiella pneumonia*, *Enterobacter*	Carbenicilline. Mecilliname
3	2.4	116	7.0	0	Pneumonia*	Not established	Cefotaxime

*Chest X-ray showed typical pneumonial changes, a bacteriological diagnosis was not established. The changes regressed after cefotaxime.

Table 2. HIV data and immunological parameters in four men with testicular cancer

			Before chemotherapy			After chemotherapy		
Patient No.	First HIV-positive sample	Risk group for HIV infection	CDC clinical state	CD4+* lymphocytes 10^9/l	CD4/CD8†	CDC clinical state	CD4+ lymphocytes 10^9/l	CD4/CD8
1	June 1986 (0)‡	Homosexual	III	1.4	0.6	III	0.7	0.8
2	July 1986 (2)	Homosexual	II	0.1	0.1	II	Refused	
3	Sept 1985 (14)	Homosexual	III	0.6	0.5	III	0.6	0.1
4	Aug 1980 (84)§	Homosexual	II	0.1	0.2			

The time in months from the first HIV-positive sample to the diagnosis of the testicular cancer is given in parentheses.
*Normal 0.5–2.5 × 10^9/l.
†Normal 1.0–4.0.
‡Sample from 1984 was negative.
§Frozen serum sample.

Four weeks after chemotherapy all three patients had normal values of haemoglobin, WBC and platelets.

The stage of the HIV infection and immunological parameters prior to and after chemotherapy are summarized in Table 2.

DISCUSSION

Out of four HIV-positive patients with testicular cancer, three received aggressive chemotherapy, as the malignant disease was stage II or III. Two patients had severe immunodeficiency. Clinically, two patients had stage II and two had stage III of the HIV infection.

Even though these patients were immunocompromised, the use of combination chemotherapy did not influence the immunological parameters in the two evaluated patients. The stage of the HIV infection had not changed after treatment. Hence it seems likely that the use of this combination chemotherapy regime does not activate the HIV infection.

During the course of the treatment one patient with severe immunodeficiency encountered septicaemia but the bacteria found were not unexpected, as they were also found in several patients in the control group.

Our observations, although only based on a few patients, indicate that leucopenia, thrombocytopenia and fever do not occur more frequently in HIV-positive patients with testicular cancer, compared to others. The treatment of testicular cancer in HIV-positive patients, therefore, does not impose greater problems than the treatment of patients who are not HIV-positive.

The main conclusion to be drawn from the present study is that the aggressive chemotherapy applied can apparently be used in the treatment of HIV-positive patients with testicular cancer, at least those without severe clinical manifestations of the infection.

Patients with testicular cancer are referred to our department from a large area, including both the capital region and rural areas. The incidence of testicular cancer in these regions is the same [1]. In contrast to this AIDS is more an urban than a rural phenomenon. Therefore the expected prevalence of proven HIV-positive patients in our patient population is difficult to establish.

Whether the observed concordance between testicular cancer and HIV infection is a chance occurrence or the relative risk is increased must be tested in a prospective study.

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