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Long-term chemotherapy of HIV-associated Kaposi's sarcoma with liposomal doxorubicin

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Abstract

The aim of this study was to examine the outcome, adverse events and clinical complications of long-term chemotherapy with pegylated liposomal doxorubicin (PegLiposomal DOX) for human immunodeficiency virus (HIV)-associated Kaposi's sarcoma (KS) in the pre-highly active antirectroval therapy (HAART) era. A phase II study over a 4-year period in a tertiary care university hospital was carried out. 52 acquired immunodeficiency syndrome (AIDS)-patients with advanced KS received long-term chemotherapy (71 ± 51 weeks) with a mean of 22.8 ± 18.2 cycles and a mean cumulative liposomal doxorubicin dose of 456 ± 364 mg/m^2 (120–1040 mg/m^2). Tumour burden, duration and dosage of PegLiposomal DOX, adverse events, opportunistic infections, immunological parameters and HIV load were measured. A complete (10%) or partial response (56%) was achieved while on chemotherapy. 10 patients (19%) showed stable disease. Tumour progression was observed in 8 patients (15%). Importantly, chemotherapy with PegLiposomal DOX was also successful after previous cytostatic therapy with bleomycin and vincristine. The most common adverse events included leucopenia, neutropenia, anaemia, and increased liver function tests. 34 patients (65%) developed new opportunistic infections and 29 patients (56%) died during the study period. To conclude, pegylated liposomal doxorubicin is a safe and effective drug for long-term chemotherapy of advanced (AIDS) KS without adverse effects on CD4 cell counts and HIV viral load.

Keywords: Kaposi's sarcoma; Pegylated liposomal doxorubicin; HIV RNA; CD4 cells; Leucopenia; Hepatotoxicity; Chemotherapy; HIV

1. Introduction

Kaposi's sarcoma (KS) is a common acquired immunodeficiency syndrome (AIDS)-defining disease caused by human herpesvirus-8 (HHV-8) [1]. In general, KS occurs as multifocal mucocutaneous lesions and afflicts internal organs such as the lymph nodes, lungs or the gastrointestinal tract [2]. In the pre-highly active antiretroviral therapy (HAART) era, the survival of patients with AIDS-KS rarely exceeded 3 years [3,4]. The management of KS depends on the extent, the degree of immunodeficiency and the existence of opportunistic infections [2,5]. At present, there is no curative treatment for HIV-associated KS although immune reconstitution and antiviral approaches have been evaluated [6,7]. Consequently, there is a need for long-term maintenance therapy. The administration of conventional cytotoxic drugs is limited because of frequent adverse effects in HIV patients prone to immunodeficiency and recurrent infections. Pegylated liposomal doxorubicin (PegLiposomal DOX) represents an improved preparation with a prolonged plasma half-life (55 h) and a 19-fold higher concentration of doxorubicin in lesional tissue [8,9].

2. Patients and methods

2.1. Patients

A total of 52 HIV patients with biopsy-proven KS received long-term chemotherapy ($\geqslant 18$ weeks) with liposomal doxorubicin from July 1992 to March 1996. Eligibility criteria included advanced KS, as defined by disseminated mucocutaneous lesions with oedema or visceral manifestation, a Karnofsky performance score $>50\%$, a white blood cell count $>2\times10^9$/l, haemoglobin >100 g/l and platelets $>50\times10^9$/l. Patients with acute opportunistic infections, Non-Hodgkin's lymphoma or cardiac failure were excluded. 85% of the

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patients were on bi-nucleoside antiretroviral therapy (either azidothymidine and didanosine or azidothymidine and zalcitabine). All patients gave written informed consent.

2.2. Treatment and evaluation

20 mg/m^2 Pegylated Liposomal DOX (Caelyx™, doxorubicin HCl liposome) were administered in 5% glucose every 2–4 weeks as a 1-h infusion. One week after the infusion and immediately before the following infusion, five target lesions, which had been selected with regard to size, colour, thickness, and surrounding oedema were clinically examined including measurement of perpendicular diameters and evaluated according to the AIDS Clinical Trial Group (ACTG) classification. The tumour volume of the target lesions was determined before and after six cycles using a 3-D ultrasound device (DUB 20-S, Taberna pro medicum, Lüneburg, Germany) [10].

In addition, laboratory tests (complete blood cell count (CBC), liver, kidney function, and HIV-RNA, Quantiplex, Bayer Diagnostics, Germany) were performed and adverse effects and opportunistic infections were documented. Laboratory results and clinical side-effects were graded according to the World Health Organization (WHO) classification. Toxic adverse events of Pegylated Liposomal DOX were treated by a dose reduction or by prolonging the treatment-free interval. For patients with a haemoglobin measurement of <80 g/l, erythropoietin or red blood cell transfusions were administered and those with less than 1000 neutrophils/μl received subcutaneous (s.c.) granulocyte-colony stimulating factor (G-CSF) = at a dose of 48 million IU.

2.3. Definition of response

The efficacy of chemotherapy was evaluated using the following criteria:

Complete response was defined as the clinical and histological disappearance of KS. Partial response was defined as a greater than 50% decrease in size or total number of the target lesions and no development of new lesions. Stable disease was defined as no significant change ($<50\%$ decrease). Progressive disease was defined as an increase in size or the development of new visceral or mucocutaneous lesions or the occurrence/increase of tumour-associated oedema.

3. Results

3.1. Patients

The majority of the 52 patients examined were Caucasian homosexual men (94%) with an average cluster of designation CD4 cell count of $75\pm106\times10^6$/l cells and a mean age of 41.7 ± 10.6 years (Table 1). Based on the ACTG criteria, a poor risk for tumour burden (T3) was noted in 82.6% of the patient population. 94.2% were at poor risk for the immune system (I3). A poor risk for systemic illness (S3) at baseline was present in 69.2%.

3.2. Treatment and response

During a median observation period of 71 ± 51 weeks (range 18–187 weeks), the 52 patients received a mean of 22.8 ± 18.2 cycles for a total of 1186 cycles. The mean cumulative doxorubicin dose accounted for 456 ± 364 mg/m^2 with 1 patient receiving a maximum of 1040 mg/m^2 (Table 1).

While on Pegylated Liposomal DOX, 34 patients (65%) responded to therapy (Table 1, Fig. 1a–d). Interestingly, 5 patients (10%) showed a complete clinical response. On histological analysis, the classical KS features (spindle-shaped cells, slit-like vessels and extravasation of red blood cells) subsided and unspecific inflammatory changes were seen (data not shown). During treatment, the lesion became HHV-8 negative as assessed by polymerase chain reaction (PCR). To assess the minimal dosage requirement for patients with a complete response, the intervals of chemotherapy were prolonged or the dosage of Pegylated Liposomal DOX was reduced to 10 mg/m^2, which led to recurrent *in loco* disease in all 5 subjects. The indicator patient has been without any sign of recurrence for more than 1 year. 10 patients (19%) showed stable disease and 8 patients (15%) developed tumour progression (Table 1).

Table 1
Characteristics, treatment and outcome of study patients

	n
Patients (all homosexual males)	52
Mean Age (years)	41.7 ± 10.6
Average CD4 cell count	$75\pm106\times10^6$/l
Patients with a poor risk for tumour burden (T3) (%)	82.6
Patients with a poor risk for immune system (I3) (%)	94.2
Patients with a poor risk for systemic illness (S3) (%)	69.2
Mean observation period	71 ± 51 (range 18–187 weeks)
Average number of cycles±S.D.	22.8 ± 18.2
Average total cumulative dose of DOX-SL±S.D.	456 ± 364 (range 1200–1040)
Patients with complete response (%)	10
Patients with partial response (%)	56
Patients with stable disease (%)	19
Patients with progression (%)	15

S.D., standard deviation.

5 patients had received therapy with bleomycin (30 mg) and vincristine (2 mg) at 3-weekly intervals prior to enrolment and had to be withdrawn due to side-effects ($n=3$) or lack of effect ($n=2$), respectively. Interestingly, 3 of the 5 patients showed a partial response and 1 patient experienced stable disease for 3 months while on Pegylated Liposomal DOX, before he suffered from massive progression.

The tumour volume regressed upon therapy with Pegylated Liposomal DOX as measured by ultrasound. After six cycles of chemotherapy, the average baseline volume of the target lesions decreased by 91% from 578 ± 623 to 52 ± 157 mm^3.

3.3. Adverse events and toxicity

The most frequent side-effects of Pegylated Liposomal DOX were granulocytopenia, anaemia, and increased liver function tests. The concomitant administration of G-CSF during 311 of 1186 cycles, the prolongation of the treatment intervals from 3 to 4 weeks, or a dose reduction to 10 mg/m^2 controlled the therapy-limiting leucopenia (Tables 2 and 3). Anaemia could be successfully managed with red blood cell transfusions or erythropoietin. The liver damage caused by cumulative doses of Pegylated Liposomal DOX was more severe (Tables 2 and 3). Since this drug is largely metabolised

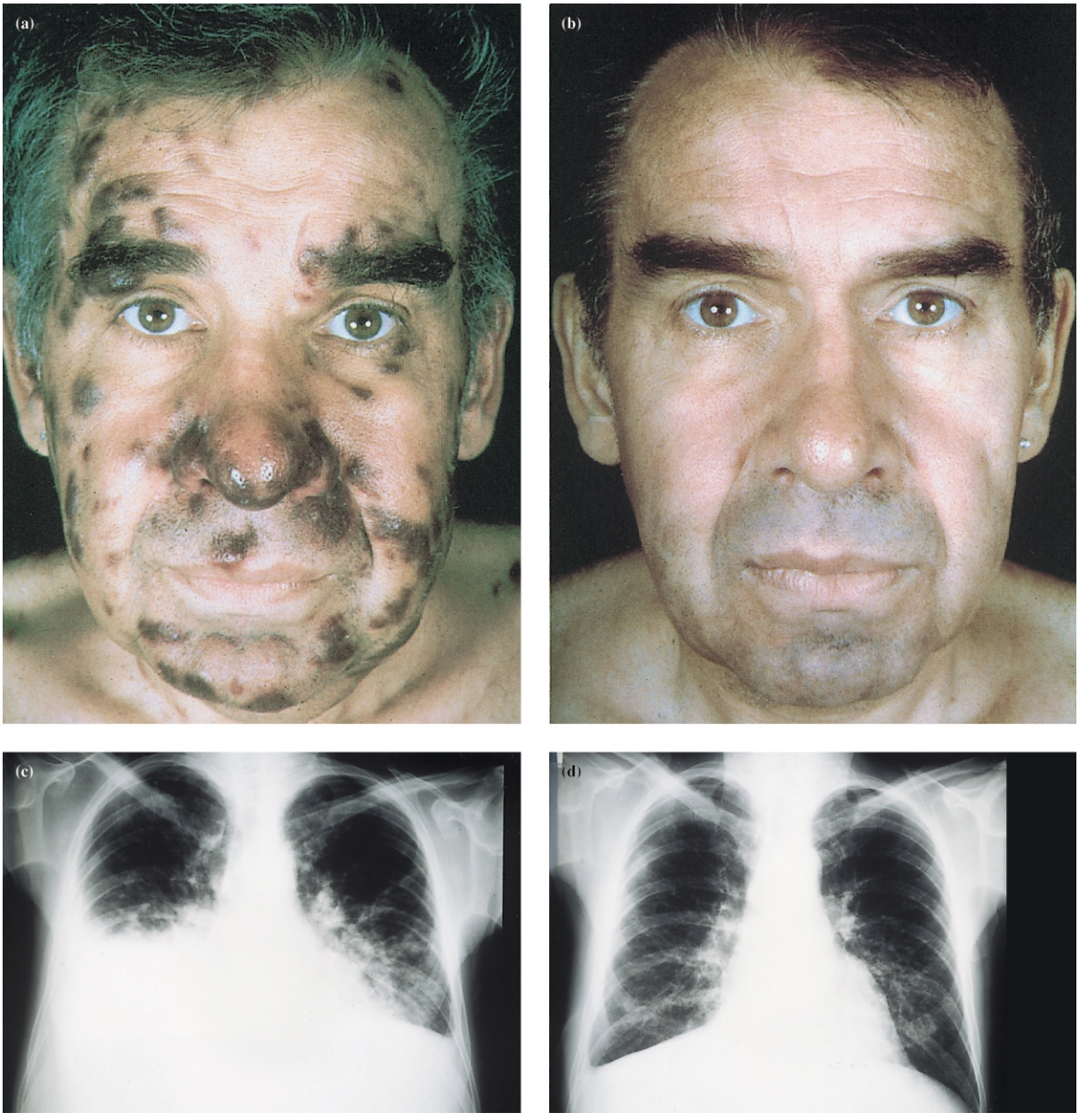

Fig. 1. Patient before chemotherapy (a) and after six cycles of liposomal doxorubicin (b). The same patient's chest X-ray before chemotherapy (c) and after 20 cycles of pegylated liposomal doxorubicin showing significant improvement of pulmonary KS and pleural effusion (d).

Table 2
Adverse events associated with Pegylated Liposomal DOX

	n	%	Grade 3/4
Leucopenia	41	79	10
Neutropenia	40	77	6
Anaemia	31	60	11
Alkaline phosphatase increase	20	38	4
Increase of liver function values	17	33	8
Polyneuropathy	17	33	0
Oedema	14	27	0
Thrombocytopenia	12	23	1
Erosive stomatitis	11	21	2
Toxic hepatosis	7	13	4
Alopecia	6	12	0
Hypoproteinaemia	5	10	0
Kidney failure	5	10	0
Myalgia	2	4	0
Gustatoric paresthesia	2	4	0
Palmar-plantar erythrodysesthesia	2	4	0
Heart failure	1	2	0
Death	29	56	

and eliminated by the liver, the most significant toxicity consisted of increased liver function values. Pegylated Liposomal DOX had to be discontinued in 7 patients (13%) for more than 8 weeks due to abnormal liver function (Table 3). After Pegylated Liposomal DOX was stopped in these patients, they experienced a rapid progression of KS, which could again be controlled following the re-administration of Pegylated Liposomal DOX.

3.4. CD4 cell counts and HIV-RNA

To assess the effects of Pegylated Liposomal DOX with regard to CD4 cells and HIV-RNA, these parameters were analysed before and 3 weeks after 47 Pegylated Liposomal DOX infusions in 17 patients. Whereas HIV-RNA remained unaffected throughout chemotherapy with a mean of 18.311 (500–128 600) prior to versus 16.258 (500–345 700) Eq/ml 3 weeks post Pegylated Liposomal DOX, CD4 cells showed a slight decline from 145 (4–401) to 124 (2–422)$\times 10^6$/l before and 3 weeks after the administration of Pegylated Liposomal DOX ($P = 0.49$, ANOVA). For comparison, HIV-RNA was analysed in 6 patients with AIDS-associated Non-Hodgkin's lymphoma receiving either COP-BLAM (cyclophosphamide, doxorubicin, vincristine, bleomycin, procarbazine; $n = 3$) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; $n = 3$). The HIV load in these patients was 100.628 and 120.879 Eq/ml and CD4 cells 242 and 177$\times 10^6$/l before and 3 weeks after the administration of one cycle, respectively.

Table 3
Laboratory abnormalities associated with Pegylated Liposomal DOX

	Pre-Pegylated Liposomal DOX $n = 52$	After 10 cycles $n = 47$
Hb (g/l)	110.2±10.9	99±13
WBC ($\times 10^9$/l)	4.2±1.7	3.1±2.6
Neutrophils ($\times 10^9$/l)	2.9±1.9	2.5±1.6
Platelets ($\times 10^9$/l)	240±120	260±160
CD4 cells ($\times 10^6$/l)	75±100	17±60
Alkaline phosphatase (IU/l)	250±110	350±300
Bilirubin (umol/l)	19.3±7	22.8±12.3
AST (IU/l)	14±13	29±40
ALT (IU/l)	18±14	23±20

WBC, white blood cell count; CD4, cluster of designation 4; AST, asparate aminotransferase; ALT, alanine aminotransferase.

Table 4
Infections during the study

	During DOX-SL therapy *n* (%)
Oral thrush	43 (83)
Pneumocystis carinii pneumonia	24 (46)
Cytomegalovirus (CMV) infection	20 (38)
Herpes simplex virus infection	17 (33)
Oral hairy leucoplakia	12 (23)
Pneumonia (other than *Pneumocystis*)	12 (23)
Candida oesophagitis/intestinal Candidiasis	11 (21)
Cerebral toxoplasmosis	11 (21)
Mycobacterium avium infection	10 (19)
Other infections	7 (13)
HIV encephalitis	7 (13)
Herpes zoster	5 (10)
Total number of patients with opportunistic infections	34 (65)

HIV, human immunodeficiency virus.

3.5. AIDS-defining events and death

A total of 34 patients (65%) developed opportunistic infections while on the study. *Pneumocystis carinii* pneumonia ($n = 24$, 46%) and cytomegalovirus (CMV) infections ($n = 20$, 38%) were the most common opportunistic infections in our patients receiving long-term chemotherapy with Pegylated Liposomal DOX (Table 4). 29 patients (56%) died during the study period (Table 2). The causes of death were intercurrent infections ($n = 20$), progression of pulmonary or gastrointestinal KS ($n = 5$), multiorgan failure ($n = 3$) and wasting syndrome ($n = 1$), respectively.

4. Discussion

Our study demonstrates a high response rate under long-term chemotherapy with liposomal doxorubicin for widespread KS in the pre-HAART era. Only 8 patients (15%) developed tumor progression during the 71±51 weeks observation period. These data are in

agreement with previous publications, which were based on much shorter observation periods [5,12–15].

In our trial, most patients received a dose of 20 mg/m^2 in 3-week intervals. The dose administered was lower than that reported by Bogner and colleagues [16], who used 40 mg/m^2 of Pegylated Liposomal DOX per month. In contrast to their study, whose median observation period was 25 weeks and median cumulative dose was only 175 mg/m^2, our patients received a cumulative doxorubicin dose of 456 ± 364 mg/m^2 during a mean observation period of 71 ± 51 weeks (18–187 weeks). In comparison, the administration of lower doses of Pegylated Liposomal DOX reduced the frequency of adverse events, while being comparably effective. However, massive progression of the KS occurred after Pegylated Liposomal DOX was discontinued. The readministration of Pegylated Liposomal DOX again controlled progressive KS, as previously reported [5].

A number of opportunistic infections unrelated to chemotherapy is to be expected in advanced HIV-patients in the pre-HAART era (CD4 cells $75 \pm 106 \times 10^6$/l), especially given the long-term follow-up. Thus, the manifestation of at least one opportunistic infection among 65% of the patients, during a mean observation period of 71 ± 51 weeks, is not surprising. The incidence of *Pneumocystis carinii* pneumonia (46%) and CMV infections (38%), however, seem strikingly high. This could be related to decreasing immunocompetence as reflected by a severe reduction in CD4 cell counts.

The cumulative toxicity caused by Pegylated Liposomal DOX represents a crucial dose-limiting factor in long-term chemotherapy. The most common adverse event was myelosuppression [5,13–15], that could have been accelerated by the antiretroviral medications (e.g. azidothymidine). Through the use of G-CSF, granulocytopenia could be successfully managed leading to a low incidence of neutropenia-associated infections. Moreover, a low incidence of acute and chronic cardiac toxicity was documented in our study following the administration of Pegylated Liposomal DOX for as long as 71 weeks. The maximum cumulative dose given to a patient in our trial was 1040 mg/m^2 without signs of a cardiopathy [16].

However, hepatotoxicity has not been previously reported during long-term application of Pegylated Liposomal DOX and was therapy-limiting in some of our patients. In a previous report, we described a case of abnormal liver function following the institution of Pegylated Liposomal DOX therapy [17]. Because of the advanced stage of HIV disease, most of the patients were on various prophylactic or therapeutic medications (e.g. pentamidine, trimethoprim sulphamethoxazole), which could also contribute to hepatotoxicity. Since HAART has been associated with hepatic problems [18], special attention has to be given to patients who receive HAART and are to be treated for KS. In comparison with conventional doxorubicin, Pegylated Liposomal DOX allows a prolonged plasma half-life and a high accumulation in tissues with compromised vasculature such as in KS [8,9]. The liposomes contain methoxypolyethylene-glycol derivatives on the surface and, therefore, will not be scavenged by the reticuloendothelial system. This explains the higher efficacy and considerably lower toxicity of liposomal doxorubicin compared with conventional doxorubicin. Pegylated Liposomal DOX has recently been identified to represent a cost-effective treatment for widespread KS [19].

Upon the implementation of HAART as a standard of care for HIV, the incidence of KS has dropped dramatically and HAART itself has been shown to make KS disappear [6,20]. Most recently, Pegylated Liposomal DOX has also been reported to help eradicate HHV-8 from KS biopsies [21]. In summary, liposomal doxorubicin represents a safe and effective drug for the long-term chemotherapy of advanced AIDS-KS without adversely affecting CD4 cell counts and HIV load.

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