Pegylated Liposomal Doxorubicin in the Treatment of Mycosis Fungoides

Dorte Lybaek and Lars Iversen
Department of Dermatology, Aarhus University Hospital, PP Orumsgade 11, DK-8000 Aarhus C, Denmark. E-mail: dortelybaek@worldonline.dk
Accepted May 16, 2006.

Sir,

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma. It typically evolves from the early patch and plaque stage to the cutaneous nodular or tumour stage and sometimes visceral involvement is seen in the later stage. MF is also present in an erythrodermic variant accompanied by lymphadenopathy and peripheral blood involvement, known as Sézary syndrome (1).

A number of different treatment modalities of MF are known. According to recently published guidelines (2, 3) they include skin-directed therapies, such as topical steroids, topical chemotherapy (nitrogen mustard and carmustine), narrow-band UVB, UVA-1 and radiotherapy, but also systemic therapy such as PUVA, methotrexate, retinoids, α-interferon, (either alone or combined with PUVA), systemic single and multi-agent chemotherapy, photopheresis, and monoclonal antibodies (e.g. anti-CD4). Doxorubicin is an antracycline, unencapsulated agent, which causes anti-neoplastic activity in a wide range of malignant diseases, especially haematologically cancers. Doxorubicin is a topoisomerase inhibitor and thereby inhibits DNA transcription and eventually causes cell death predominantly in cancer cells, as they have a higher concentration of topoisomerase enzyme than normal cells. It has a low therapeutic index and haematological toxicity is a common and dose-dependent side-effect. Antracycline-induced cardiomyopathy can be irreversible and lead to congestive heart failure. The frequency of this side-effect is related to the cumulative doses of doxorubicin, which should not exceed 450–550 mg/m^2 (4).

Pegylated liposomal doxorubicin (LD) has a significantly different pharmacokinetic profile from the unencapsulated agents, and is associated with prolonged half-life, altered toxicity profile, and the possibility of enhanced anti-tumour activity (5).

The efficacy of LD in the treatment of MF has been described in one retrospective multicentre study (6) two single-centre studies (7, 8) and two case reports (9, 10). The majority of studies have reported high efficacy of LD monotherapy in patients with MF (4–7), although this has been questioned by others (10).

Here we report the outcomes and adverse effects in 6 patients all diagnosed with MF stage IB, IIB or IVA and treated with LD (CAELYX™, Schering Plough Pharmaceuticals, Farum, Denmark).

CASE REPORT

Six patients were treated with LD (Table I). All patients had histologically confirmed MF at either stage IB, IIB or IVA, as defined according to the EORTC/BMFT Cutaneous Lymphoma project group (11). All patients had failed on at least three other treatment modalities prior to treatment with LD.

Two patients with MF stage IB received doxorubicin, although systemic chemotherapy is not recommended as a standard

Table I. Demographic data on patients diagnosed with mycosis fungoides. Outcome of treatment with pegylated liposomal doxorubicin (LD) 20 mg/m^2 every third week

Patient	Sex/age (years)	TNPBM stage	Pre-LD therapy	Results	Toxicity and grade	Total doses	Response duration (months)	Post-LD therapy
1	M/58	IVA	TS, CS, acitretin, cyclophosphamide, anti-CD4, electron-beam therapy	CR		8	5	MTX
2	F/82	IB	TS, acitretin, nitrogen mustard, MTX	PR	Palmoplantar erythrodysesthesia, 1	4	3	Acitretin
3	M/83	IB	TS, CS, acitretin, MTX, nitrogen mustard, PUVA, photopheresis, anti-CD4	PR	Vertigo, 2; cardiac failure function, 3	7	9	TS
4	M/56	IIB	TS, CS, PUVA, nitrogen mustard, MTX, acitretin, leukeran, anti-CD4, electron-beam therapy, radiotherapy	SD		10		TSEB
5	M/70	IIB	TS, nitrogen mustard, MTX	PR	Cardiac ischaemia, 3; dermatitis, 2; pneumonia, 2	10	9	MTX
6	F/83	IIB	TS, CS, nitrogen mustard, MTX, acitretin, electron-beam therapy, cyclophosphamide	PR	Lymphopaenia, 2	9	5	Acitretin

TNPBM: staging criteria, including tumour status, lymph node status, peripheral blood involvement, and metastatic status; TS: topical steroids; CS: corticosteroids systemic; MTX: methotrexate; PUVA: ultraviolet A photochemotherapy with 8-methoxypsoralen; anti-CD4: fully human monoclonal anti-CD4 antibody; TSEB: total skin electron beam. Response duration was measured for all patients who achieved a complete remission (CR) or a partial remission (PR) from the first documentation of response to the time of disease recurrence or progression. SD: stable disease – as any response that did not meet the criteria for CR, PR or disease progression.

 ISSN 0001-5555
DOI: 10.2340/00015555-0133

treatment of MF in the early stage. However, previous studies (7) have used LD for patients with relapsing or recalcitrant cutaneous T-cell lymphoma stage IA and IB with the outcome of complete response.

Patient 2 had severe disease progression, and an increased body surface area was involved. There was a lack of effect of topical steroids, acitretin, nitrogen mustard, MTX and due to logistic problems UVB/PUVA was not manageable. Patient 3 had also tried several treatment modalities, as shown in Table I.

Before treatment and every third week during treatment with LD patients were monitored by clinical examination, ECG and a routine laboratory test including haemoglobin, leucocytes with differentials, platelets, alanine aminotransferase, alkaline phosphatase, bilirubin, albumin, potassium, sodium, creatinine, carbamide and prothrombin time. LD was administered intravenously at a dose of 20 mg/m^2 every third week, with a maximum of 10 cycles.

Side-effects were classified according to Common Toxicity Criteria Version 2.0.

Complete response (CR) was defined as the absence of residual disease. Partial response (PR) was defined as a 50% or greater decrease in the size of the pre-existing lesions. Disease progression was defined as more than a 25% increase in the diseased skin involvement. Stable disease was defined as any response that did not meet the criteria for CR, PR or disease progression. Response duration was measured for all patients who achieved a CR or a PR from the first documentation of response to the time of disease recurrence or progression.

Among the six patients treated, patient 1 (Table I) obtained a CR after 8 doses of LD (Fig. 1). Before treatment with LD was started, a computerized tomography scan was performed demonstrating enlarged lymph nodes (> 1.5 cm) in the axillae. Enlarged lymph nodes were also detectable during clinical examination, but disappeared after the last dose of LD. Approximately 4 months after the treatment was stopped new skin lesions appeared, and the patient started treatment with methotrexate.

Four patients (patients 2, 3, 5 and 6) achieved PR after 4–10 doses of LD. The response duration time was 3–9 months. When treatment with LD was stopped, patients were treated with acetritin, topical steroids or methotrexate (Table I).

One patient (no. 4) experienced a stable disease with no response even after 10 doses of LD. None of the 6 treated patients showed clinically disease progression or developed new pathologically suspect lymph nodes (lymph node biopsy was not performed). Generally the treatment was well tolerated. The major toxicity was grade 3: cardiac failure and cardiac ischemia, grade 2: lymphopaenia, pneumonia, dermatitis and vertigo and grade 1: palmoplantar erythrodysesthesia.

Patient 2 stopped and patient 3 was withdrawn from the treatment with LD after 4 and 7 doses, respectively, due to palmoplantar erythrodysesthesia and cardiac failure.

DISCUSSION

Wollina et al. (8) first reported LD for the treatment of cutaneous T-cell lymphoma in 2000. They also investigated 6 patients and found an overall response rate of 83%, which is similar to the results obtained in this study (response rate 83%, 5 out of 6 patients). In the study by Wollina et al. (8) the response duration time was not determined. Long-term remission of tumour-stage MF following treatment with LD has been reported in a case report of one patient (9), who remained in complete remission 21 months after treatment was started. In our patient group disease recurrence or progression was seen after 3–9 months.

The most extensive study of LD in the treatment of cutaneous T-cell lymphoma is a recent retrospective multicentre study with 34 patients with recurrent or recalcitrant MF (stage II–IVA) (6). Here LD was found to be effective and safe and it resulted in a response rate of 88% and a response duration time of ≥1–44 months.

As mentioned previously, the effect of LD in the treatment of cutaneous T-cell lymphoma, especially MF, has been reported only in single-centre studies (7, 8), case reports (9, 10) and one retrospective multicentre study (6), and in the case report by Prince et al. (10) who found no evidence of objective response after treatment with LD of two patients with MF. However, our results are in accordance with most other reports suggesting efficacy of LD as monotherapy in patients with cutaneous T-cell lymphoma. However, a major aim of additional studies is to perform a large-scale, prospective, multicentre study in order to prove a significant effect of LD in the

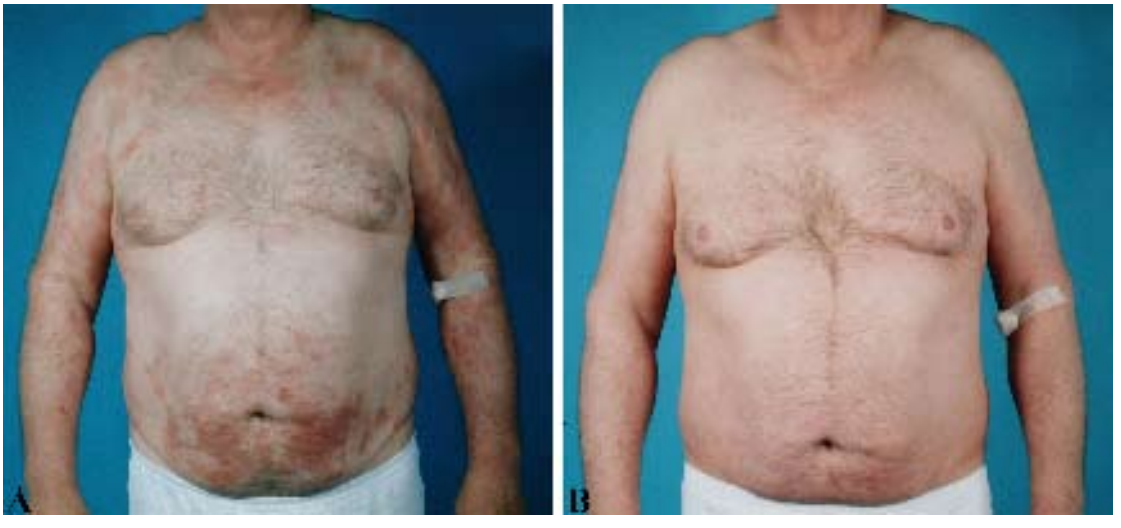

Fig. 1. Patient 1: (A) before treatment with pegylated liposomal doxorubicin; and (B) after eight doses.

treatment of cutaneous T-cell lymphoma. Interestingly, such an European Organisation for Research and Treatment of Cancer-supported study is ongoing and may be completed soon.

LD seems to be well tolerated, with a low rate of severe adverse effects compared with other chemotherapy protocols in patients with cutaneous T-cell lymphoma. However, one important side-effect is cardiomyopathy, which is related to the cumulative dose of doxorubicin. Due to this side-effect, there is a limitation to the total doses of LD that can be given. Another very important study is therefore to clarify whether patients could benefit from adjuvant treatment while being treated with LD and to define the best treatment regime after patients have achieved a PR or CR with LD.

Conflict of interest: The authors have no conflict of interest.

REFERENCES

1. Diamandidou E, Cohen PR, Kurtzrock R. Mycosis fungoides and Sézary syndrome. Blood 1996; 88: 2385–2409.
2. Whittaker SJ, Marsden JR, Spittle M, Russel Jones R. Joint British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol 2003; 149: 1095–1107.
3. Dummer R. Emerging drugs in cutaneous T-cell lymphomas. Expert Opin Emerg Drugs. 2005; 10: 381–392.
4. Hotobàgyi GN. Anthracyclines in the treatment of cancer: an overview. Drugs 1997; 54 (suppl) 1–7.
5. Crawford J. Clinical uses of pegylated pharmaceuticals in oncology. Cancer Treat Rev 2002; 28 (suppl): 7–11.
6. Wollina U, Dummer R, Brockmeyer NH, Konrad H, Busch JO, Kaatz M, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. Cancer 2003; 98: 993–1001.
7. Di Lorenzo G, Di Trolio R, Delfino M, De Placido S. Pegylated liposomal doxorubicin in stage IVB mycosis fungoides. Br J Dermatol. 2005; 153: 183–185.
8. Wollina U, Graefe T, Krate K. Treatment of relapsing or recalcitrant cutaneous T-cell lymphoma with pegylated liposomal doxorubicin. J Am Acad Dermatol 2000; 42: 40–46.
9. Tsatalas C, Martinis G, Margaritis D, Spanoudakis E, Kotsianidis I, Karpouzis A, Bourikas G. Long-term remission of recicalcitrant tumour-stage mycosis fungoides following chemotherapy with pegylated liposomal doxorubicin. J Eur Acad Dermatol Venereol 2003; 17, 80–82.
10. Prince HM, Seymour JF, Ryan G, McCormack C. Pegylated liposomal doxorubicin in the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 2001; 44: 149–150.
11. Kerl H, Sterry W. Classification and staging. In: Burg G, Sterry W, eds. EORTC/BMFT Cutaneous Lymphoma Project Group: recommendations for staging and therapy of cutaneous lymphomas. Berlin: Springer, 1987: p. 1–10.