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# Liposomal chemotherapy in cutaneous T-cell lymphomas: current status and future prospects

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A B S T R A C T

Liposomes are lamellar structures composed of a lipid bilayer. They are used as carriers for different drugs. The present paper reviews the use of intravenous liposomal anticancer drugs in dermato-oncology. The broadest application is found today for liposomal anthracyclines, i.e. doxorubicin and daunorubicin. There is clear evidence for liposomal drug efficacy and safety cutaneous T-cell lymphoma (CTCL) with response rates about 80-90%. Randomized, double-blinded prospective controlled trials are on the way.

Liposomes were discovered in 1961<sup>1</sup> and their potential as drug delivery systems and vehicles cytotoxic drugs was rapidly appreciated.<sup>2</sup> The liposomal-encapsulated cytotoxic drugs have a number of potential advantages over the corresponding unencapsulated agents. The liposome prolongs the half-life of the drug in the circulation and alters its biodistribution pattern such that drug deposition is increased in tumour tissue and decreased in certain dose-limiting normal tissues.<sup>3</sup>

This review shall confine itself to a description of the current status of liposomal cytotoxic drugs in cutaneous T-cell lymphoma.

## Pharmacokinetic and biodistribution studies

An enormous number of liposomal preparations have been subjected to preclinical analysis in animal models.<sup>3</sup> Of these only a small number have advanced to the stage of formal clinical appraisal.

The liposomal formulation that has entered clinical studies as DaunoXome has been subjected to extensive evaluation. For these studies, neutral phospholipid liposomes were formulated from distearoyl phosphatidylcholine, cholesterol and the ionophore A23187 in a ratio of 2:1:0.004. The liposomes had a median diameter of 77 nm and contained nitrilotriacetic acid which was radiolabelled with <sup>111</sup>In prior to

administration. Turner *et al.*<sup>4</sup> injected such vesicles containing 18.5 MBq of liposome-encapsulated radioactivity into 24 patients with a variety of tumours (including one patient with melanoma). Pharmacokinetic analysis revealed approximately 50% of the injected dose remaining in the circulation at 4 hours and 20% at 24 hours. Gamma camera imaging at 24 and 48 hours demonstrated positive tumour images in 22 of the 24 patients. There was evidence of significant uptake in the liver (34±19% of the injected dose) and spleen (4.9±3.4% of the injected dose) from region of interest analysis. In a further report dealing with the same group of patients, data were presented for two patients who underwent surgery at 7 and 10 days after the liposome infusion.<sup>5</sup> Tumour to blood ratios between 6.5 and 18.3:1 were reported for the primary tumour and lymph node and liver metastases. Present *et al.*<sup>6</sup> presented data on two patients with AIDS-related Kaposi's sarcoma and non-Hodgkin's lymphoma whose lesions were successfully imaged with the same <sup>111</sup>In-NTA-labelled liposomes, although no data relating to pharmacokinetic parameters or biodistribution were presented.

In a similar fashion, the pegylated liposomal formulation that is currently under clinical investigation as Caelyx/Doxil, has been subjected to a number of studies. Gabizon *et al.*<sup>7</sup> assessed the pharmacokinetics of equivalent doses of unencapsulated

and/or pegylated liposomal doxorubicin in 7 patients. Another 9 patients received the liposomal drug alone. Plasma elimination of the pegylated liposomal agent followed a biexponential curve with median  $t_{1/2\alpha}$  and  $t_{1/2\beta}$  of 2 and 45 hours, respectively. The drug detected in the plasma was exclusively in the liposomal form, confirming the stability of this agent *in vivo*. Both the plasma clearance (0.1 litres/h vs 45 litres/h) and the volume of distribution (4 litres vs 254 litres) were significantly lower for the liposomal compared to the unencapsulated drug. In a number of patients, the doxorubicin concentration in the fluid from malignant effusions was measured and was shown to be increased 4-16-fold for the liposomal agent, reaching a peak between 3 and 7 days after drug administration. Northfelt *et al.*<sup>8</sup> demonstrated the ability of Caelyx/Doxil to target cutaneous AIDS-related Kaposi's sarcoma lesions in 18 patients. The subjects were randomly allocated to receive either Caelyx/Doxil or unencapsulated doxorubicin and representative lesions were biopsied 72 hours later. The doxorubicin level in the Kaposi's sarcoma lesions was 5.2 to 11.4 times greater in those patients treated with the pegylated liposomal form of the drug. Detailed pharmacokinetic analysis confirmed revealed that the drug was essentially confined within the circulation with a volume of distribution of 2.2 to 4.4 litres/m<sup>2</sup>. The  $t_{1/2\alpha}$  and  $t_{1/2\beta}$ , were 3.8 and 41.3 hours, respectively. A detailed analysis of the biodistribution and pharmacokinetics of <sup>111</sup>In-DTPA-labelled pegylated liposomes in 17 patients with locally advanced cancers has recently been published.<sup>9</sup> The  $t_{1/2\beta}$  of radiolabelled liposomes was 76.1 hours. Positive tumour images were obtained in 15 of 17 studies (4/5 breast cancer, 5/5 head and neck cancer, 3/4 lung cancer, 2/2 glioma and 1/1 cervix cancer). The levels of tumour liposome uptake estimated from regions of interest on gamma camera images were approximately 0.5-3.5 % of the injected dose at 72 hours. The levels of tumour uptake were greatest in the patients with head and neck cancers, intermediate in the patients with lung cancers and relatively low in the patients with breast cancers. Significantly, the liposome uptake values were inversely correlated with the estimated tumour volumes of the various tumour types. In a further patient with extensive mucocutaneous AIDS-related Kaposi's sarcoma, prominent deposition of the radiolabelled liposomes was seen within the lesions. In two patients with resectable head and neck cancer samples of the tumour and adjacent normal tissue were obtained at operation. The levels of tumour

uptake exceeded those in adjacent normal tissues by between 2.3-10.8-fold.

## Clinical trials of liposomal cytotoxic drugs

### Liposomal doxorubicin (TLC D-99, Evacet)

TLC D-99 (The Liposome Company, Princeton, New Jersey, USA) consists of doxorubicin encapsulated in liposomes composed of egg phosphatidylcholine and cholesterol (ratio 1.22:1). Pharmacokinetic, phase I, II and III clinical trials have been conducted with this agent.<sup>10-14</sup> In a randomised phase II trial, 40 patients with AIDS-related Kaposi's sarcoma received either 10 mg/m<sup>2</sup> (19 patients) or 20 mg/m<sup>2</sup> (21 patients) of TLC D-99 every 2 weeks. There were partial responses in 15% (6 of 40) of patients and a further 65% (26 of 40) achieved disease stabilisation. Response to treatment was related to dose with 5% (1 of 19) of patients in the low-dose group achieving a response in comparison to 24% (5 of 21) of patients in the high-dose group. The major toxicity was haematological, with neutropenia occurring in 68% and 81% of patients in the low- and high-dose groups, respectively. Alopecia was reported in only 8% of patients and other non-haematological toxicities were mild.<sup>13</sup>

### Liposomal daunorubicin (DaunoXome)

DaunoXome (NeXstar Pharmaceuticals Inc., San Dimas, USA) is a daunorubicin-containing small unilamellar vesicle of 50-80 nm diameter composed of distearoyl phosphatidylcholine and cholesterol in a molar ratio of 2:1. In a phase I/II pharmacokinetic and clinical analysis, this agent has been shown to alter the pharmacokinetic profile of the drug favourably to that of the unencapsulated drug.<sup>15</sup> At the 80 mg/m<sup>2</sup> dose level, the mean total body clearance (6.6 vs 233 mL/min) and volume of distribution (2.9 litres vs 1055 litres) were significantly lower for liposomal, as compared to unencapsulated, daunorubicin. Such data translate to a 36-fold increase in the area under the time:concentration curve for the liposomal agent. Initial phase II studies of DaunoXome were conducted in patients with AIDS-related Kaposi's sarcoma who were treated at doses ranging from 40 to 60 mg/m<sup>2</sup> every two weeks. Response rates in the order of 40-73% were documented.<sup>15-18</sup> In a subsequent phase III study 232 patients with AIDS-related Kaposi's sarcoma received either DaunoXome 40 mg/m<sup>2</sup> or standard combination chemotherapy (ABV - doxorubicin 10 mg/m<sup>2</sup>, bleomycin 15 IU, vincristine 1 mg) every 2 weeks.<sup>19</sup> Equivalent response rates were reported for the two treat-

ment arms (25% and 28%, respectively). DaunoXome caused significantly less neuropathy (13% versus 41%) and alopecia (8% versus 36%) than ABV but slightly more myelosuppression (Grade 3 neutropenia 36% vs 36%, Grade 4 neutropenia 15% vs 5%). The incidence of opportunistic infections was increased amongst the patients treated with DaunoXome (36% vs 26%) but this did not reach statistical significance.

Thus far, there have been few studies of DaunoXome in patients with tumours other than Kaposi's sarcoma.

### **Pegylated liposomal doxorubicin (Caelyx/Doxil)**

Very extensive clinical evaluation has been conducted with Caelyx/Doxil (Alza Corp., Mountain View, USA), which consists of doxorubicin encapsulated in a small unilamellar vesicle of mean diameter 96 nm. The liposome matrix is composed of hydrogenated soybean phosphatidylcholine (56.2%), cholesterol (38.3%), and N-(carbamoyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycerol-3-phosphoethanolamine sodium salt (5.3%). Initial evaluation of Caelyx/Doxil was performed in patients with AIDS-related Kaposi's sarcoma with response rates of 69-93%.<sup>20-22</sup> Subsequently, two large Phase III studies were conducted comparing Caelyx/Doxil to standard combination chemotherapy. 23, 24 In the first study, 241 patients received 6 cycles of either Caelyx/Doxil (20 mg/m<sup>2</sup>) or bleomycin (15 IU/m<sup>2</sup>) and vincristine (2mg) every 3 weeks.<sup>23</sup> The response rate for Caelyx/Doxil (59%) was significantly greater than bleomycin and vincristine (23%). In addition, treatment with bleomycin and vincristine was significantly more toxic as measured by the need to discontinue treatment prematurely (27 vs 11%) or the incidence of peripheral neuropathy (14% vs 3%) and leukopenia (51 vs 72%). In the second study, 258 patients received 6 cycles of either Caelyx/Doxil (20 mg/m<sup>2</sup>) or doxorubicin (20 mg/m<sup>2</sup>), bleomycin (10 IU/m<sup>2</sup>) and vincristine (1 mg) every 2 weeks.<sup>24</sup> Caelyx/Doxil was significantly more effective than the combination regimen, with response rates of 45.9% and 24.8%, respectively. Caelyx/Doxil was better tolerated than the combination in terms of alopecia (1 vs 19%), nausea and vomiting (15 vs 34%) and neuropathy (6 vs 14%), although there was no difference in grade 3 leukopenia (36 vs 42%). These data must be viewed in light of the limited activity of single agent unencapsulated doxorubicin against AIDS-related Kaposi's sarcoma.<sup>25</sup>

The ability of Caelyx/Doxil to ameliorate the familiar side effects of unencapsulated doxorubicin

has also been widely reported. Nausea and vomiting<sup>23,26</sup>, alopecia<sup>23,24,26</sup>, local tissue vesicant activity<sup>26,27</sup> and doxorubicin-induced cardiomyopathy<sup>28-30</sup> are all significantly reduced by encapsulation of the drug in pegylated liposomes. However, the administration of repeated doses of Caelyx/Doxil is associated with a novel toxicity, plantar-palmar erythrodysesthesia (PPE) or *hand-foot* syndrome, which manifests as painful swelling and inflammation of the hands and feet, intertriginous areas and sites of trauma.<sup>31-33</sup> A similar mucosal toxicity associated with superficial mouth ulcers also occurs. As mentioned above, these mucocutaneous manifestations have been shown to be dose-limiting in many studies. A number of attempts have been made to define therapies to limit this toxicity, including the use of pyridoxine,<sup>34</sup> ergotamine,<sup>35</sup> topical dimethylsulfoxide<sup>36</sup> and amifostine.<sup>37</sup> Such interventions offer the prospect of allowing larger doses of Caelyx/Doxil to be administered safely but, as yet, none has been shown to be effective in a randomised study.

### **Liposomal drug formulations in dermatological and oncological practice**

Liposomes in dermatology are quite popular in topical use for recovery of horny layer barrier function. Even empty liposomes seem to have an effect in under this view. Investigations were carried out on encapsulation of different compounds into liposomes such as econazole, dithranol/anthralin, vitamin-D3-derivates<sup>38,39</sup> hydroxyzine,<sup>40</sup> cyclosporine A,<sup>41</sup> paromycin,<sup>42</sup> acyclovir,<sup>43</sup> amphotericin B,<sup>44</sup> ultraviolet light filters,<sup>45</sup> and anaesthetics<sup>46</sup> among many others and their pharmacologic and pharmacokinetic qualities.

### **Lessons learned from Kaposi's Sarcoma**

The longest experience with liposomal anthracyclines exists in in patients with advanced AIDS-related Kaposi's sarcoma. Here pegylated liposomal doxorubicin monotherapy achieved overall response rates ranging from 46 to 77% in randomized trials with a marked improved safety profile compared to traditional chemotherapy protocols (bleomycin, Vincristine, free doxorubicin).<sup>47</sup>

In a prospective multicenter study, liposomal doxorubicin was used in AIDS-related Kaposi's sarcoma in patients receiving highly active antiretroviral treatment (HAART). Patients with more than 10 cutaneous lesions or visceral disease were treated with 20 mgm<sup>-2</sup> liposomal doxorubicin every 3 weeks. The overall response rate

was 78% and the combination with HAART was well tolerated.<sup>48</sup>

Recently a phase IV trial with liposomal daunorubicin (DaunoXome) had been completed.<sup>49</sup> Ninety-four patients were eligible. Daunorubicin was administered as single chemotherapy to 70% of the patients with a mean of 16 treatment cycles per patient. Overall response was 38%. No severe cardiotoxic event was observed despite high cumulative doses and prolonged follow-up. Ninety percent of patients also received HAART.

The other question that raised in combining anticancer drugs with HAART is whether the immunologic response to antiviral therapy is altered. In a study with<sup>50</sup> patients using liposomal anthracyclines with HAART there was no significant loss of CD4 or CD8 cells or an increase in HIV-1 viral load during or up to 12 months after chemotherapy.<sup>50</sup>

In conclusion, liposomal anthracyclines are the treatment of choice in cases with disseminated or visceral lesions. Furthermore, the combination of liposomal anthracyclines with HAART in AIDS-related Kaposi's sarcoma is safe and well tolerated.

#### Cutaneous T-cell lymphoma (CTCL)

Cutaneous T-cell lymphomas (CTCL) are neoplasias of malignant T-lymphocytes that usually represent a helper/inducer phenotype. Since a specific homing of the malignant cells occurs within the epidermis, chemotherapeutics should concentrate in skin tissue to achieve the best possible activity. On the other hand, there is no curative treatment available. All treatments aim to control the disease. Therefore the impact of treatment on quality of life has to be considered more than in curative attempts.

The use of liposomal anthracyclines in CTCL was based on the positive results for liposomal doxorubicin in polychemotherapy protocols for non-Hogkin's lymphoma. For CTCL, however, it could be demonstrated that liposomal anthracyclines are effective as monotherapy. Pegylated liposomes seem to offer a particular benefit because of their concentration in skin.

In a pilot study with six patients of CTCL of the mycosis fungoides type, stage Ib/IIb, 20 mgm<sup>-2</sup> liposomal doxorubicine (Caelyx/Doxil) were given intravenously once a month. Patients achieved 6 to 8 doses and the final outcome was a complete response in 4 patients and a partial response in one: overall response rate 83%.<sup>51</sup>

In a larger study on ten patients stage Ib to IVb these results could be confirmed with an overall response rate of 80% and an overall survival of

19.8±7.4 months (mean ± standard deviation).<sup>52</sup> Another report supported the data. A woman with mycosis stage IIb unresponsive to several therapeutic modalities was treated successfully with liposomal doxorubicin (Caelyx/Doxil).<sup>53</sup>

By galectin fingerprinting we found evidence that the altered growth control of malignant T-cells in CTCL could be partially restored with liposomal doxorubicin.<sup>54</sup>

In a multicenter trial on 34 patients with CTCL stages I to IV different doses from 20 to 40 mgm<sup>-2</sup> liposomal doxorubicine (Caelyx/Doxil) were given every two to four weeks. The final outcome was characterized by a high response rate of 88.2% with a mean overall survival of 17.8±10.5 months.<sup>55</sup> The higher doses did not result in better response rates but more side effects. The shortage of intervals, e.g. from once a month to twice a month, did not provide better results. Adverse effects were seen in 41.2% of patients, but only 6 patients had adverse effects of grade 3 or 4 according to the WHO classification of adverse effects. There was no treatment related death. One patient had a capillary leak syndrome with a delay of several days after a single infusion of liposomal doxorubicin.

In a pilot study using liposomal daunorubicin 20 mgm<sup>-2</sup> (DaunoXome) once a month in tumour stage CTCL two partial and one complete responses were achieved.<sup>56</sup> The survival was more than 10 months in a patient with complete response and 6 or more than 8 months in the two remaining patients.

In conclusion, liposomal anthracyclines offer a great advantage compared to the free drugs in CTCL. No cardiotoxicity was observed and complete responders may have remission for years. The overall response rate is comparable or even superior to polychemotherapy protocols with a better safety and quality of life. However, no prospective controlled trial has been performed yet.

#### Conclusions and outlook

After relatively slow progress in the first three decades after their discovery, liposomes are now undergoing a period of intensive clinical development. A large number of phase I/II trials have shown that liposomal drugs have activity as single agents against a variety of treatment refractory tumours. First evidence has gained for dermatological tumours with best evidence in AIDS-related Kaposi's sarcoma. Recently, liposome anthracyclines have been introduced to CTCL-treatment. This treatment modality is a safe and effective 2<sup>nd</sup>-line therapy in CTCL. Prospective con-



trolled, double-blinded randomized studies are performed now. In addition to the existing application of liposomes as vehicles for cytotoxic drugs, new targeting approaches (for immuno-, radio- or gene-therapy) offer an exciting opportunity to widen their scope in the treatment of malignant disease.

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