Prospective Multicenter Study of Pegylated Liposomal Doxorubicin Treatment in Patients With Advanced or Refractory Mycosis Fungoides or Sézary Syndrome

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Objective: To assess the rate of objective response to pegylated liposomal doxorubicin hydrochloride (Caelyx) in patients with advanced or refractory cutaneous T-cell lymphoma (CTCL).

Design: Prospective, open, multicenter study.

Setting: Thirteen dermatology departments in France.

Patients: Twenty-five patients with either (1) stage II to stage IV CTCL previously unsuccessfully treated with at least 2 lines of treatments or (2) histologically transformed epidermotropic CTCL requiring chemotherapy.

Intervention: Administration of Caelyx intravenously once every 4 weeks at a dose of 40 mg/m².

Main Outcome Measures: The response to treatment was evaluated by clinical evaluation.

Results: At the end of treatment, we observed an objective response (primary end point) in 56% of the patients (14 of 25): 5 complete responses and 9 partial responses. The median overall survival time was 43.7 months. For the 14 patients who experienced an objective response, the median progression-free survival time after the end of treatment was 5 months.

Conclusions: This prospective study demonstrates the effectiveness of Caelyx in treating CTCL, with an overall response rate of 56% in spite of the high proportion of patients with advanced-stage disease. Responses were observed in 2 subpopulations of patients in which the prognosis is known to be poorer: Sézary syndrome (overall response rate, 60%) and transformed CTCL (overall response rate, 50%). Moreover, this study shows that dose escalation to 40 mg/m² does not seem to improve the effectiveness but increases toxic effects (especially hematologic toxic effects) compared with the dose previously tested of 20 mg/m².

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CUTANEOUS T-CELL Lymphomas (CTCLs) are neoplasias of malignant T lymphocytes. Mycosis fungoides (MF) is the most common type of CTCL and is considered an indolent type. In the early stages (IA and IB), the prognosis is excellent, with survival similar (IA) or close (IB) to that of an age-, sex-, and race-matched population. At these stages, treatments consist of phototherapy, local steroids, or local chemotherapy (nitrogen mustard and carmustine). In more advanced stages (IIB, III, and IV), the prognosis becomes poorer, and the CTCLs are often resistant to treatments. At these stages, most of the guidelines recommend as first-line treatments immunomodulators such as interferon-alfa and retinoids or rexinoids, low doses of methotrexate, radiotherapy, and extracorporeal photopheresis (for Sézary syndrome [SS]) to avoid increasing patients’ high infection sensitivity.

The second-line recommendations are to use more aggressive systemic therapies such as chemotherapy (cyclophosphamide, cisplatin, vincristine, or etoposide), which cause numerous adverse effects (especially infectious complications and hematologic toxic effects) and have no proven effect on survival. Among these chemotherapies, doxorubicin hydrochloride is the most commonly used anthracycline for advanced stages of CTCL. It induces hematologic dose-
dependent toxic effects and may lead to cardiomyopathy. Pegylated liposomal doxorubicin is a new formulation of doxorubicin encapsulated in liposomes to achieve pharmacokinetic properties such as lower plasma concentration peak, lower clearance, smaller distribution volume, and longer half-life.7,12 The size of the liposomes allows selective accumulation in the tumor vascular bed, and the pegylation induces reduced clearance by the mononuclear phagocyte system. Increased penetration into the tumor and longer presence owing to liposomal encapsulation could attenuate the toxic effects and allows equal or even enhanced efficacy of the parent anthracycline. In Kaposi’s sarcoma, breast cancer, and ovarian cancer,11 pegylated liposomal doxorubicin has been shown to be less cardiotoxic and nephrototoxic than other forms of doxorubicin.14,15

Wollina et al16 first used pegylated liposomal doxorubicin in 6 patients with CTCL and observed an overall response rate of 83% (4 patients with complete response [CR] and 1 with partial response [PR]) with very few adverse effects (1 case of asymptomatic cardiac ischemia, 1 of viral upper airway infection, 5 of anemia, and 3 of lymphopenia). These results were confirmed in a multicenter retrospective study of 34 patients with CTCL.17 The aim of the present study is to confirm these results in a prospective, open, multicenter study using pegylated liposomal doxorubicin hydrochloride (Caelyx; Schering-Plough, Kenilworth, New Jersey) once every 4 weeks at a dose of 40 mg/m² in patients with CTCL.

METHODS

PATIENT ELIGIBILITY

This prospective multicenter study was conducted in 13 dermatology departments in France. The patients were between 18 and 75 years of age, had a performance status of 2 or higher by the Eastern Cooperative Oncology Group (ECOG) criteria,18 and also had a histologically proven CTCL of 1 of the 2 following types: (1) MF and SS, involving stage II (T1-T3N1M0) to stage IV (T1-T4N2-N3M0-M1) disease previously unsuccessfully treated by at least 2 lines of treatment including topical Carmustine, topical nitrogen mustard, UV therapy (UV-B and psoralen–UV-A), total body electron therapy, radiotherapy, interferon-alpha, retinoids, monoclonal antibody, or polychemotherapy; or (2) transformed MF and SS involving CD30⁺ or CD30⁻ large cell CTCL requiring chemotherapy. The CTCL subtypes were classified according to the European Organization for Research and Treatment of Cancer (EORTC) criteria,19 and CTCL stages were defined according to the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas.20 We defined Sézary syndrome by using the triad of erythroderma, generalized lymphadenopathy, and the presence of Sézary cells in the peripheral blood. It also had to meet the criteria of the International Society for Cutaneous Lymphomas (ISCL):21 an absolute Sézary cell count of at least 1000 cells/mL, a CD4/CD8 ratio of 10 or higher, an increased number of circulating T cells with aberrant marker expression, and evidence of T-cell clones in the peripheral blood detected by molecular or cytogenetic methods.21

The biological inclusion criteria were a polymorphonuclear neutrophil count higher than 1.5 × 10⁹/L; platelet count higher than 100/µL; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase concentrations less than 2.5 times those of the upper limit of normal; bilirubin level below the upper limit of normal; and creatinine concentration lower than twice the upper limit of normal. (To convert neutrophils to number of cells × 10⁹/L, multiply by 0.001; platelets to number of cells × 10⁹/L, multiply by 1.0.)

Included patients had to have good heart function (left ventricular ejection fraction ≥50%). The main exclusion criteria were unstable heart disease, history of another malignant neoplasm, active infection, previous treatment with doxorubicin hydrochloride at a cumulative dose higher than 300 mg/m², previous treatment with doxorubicin without effectiveness, previous treatment with more than 1 line of chemotherapy in CD30⁺ or CD30⁻ large-cell CTCL, concomitant radiotherapy, and/or pregnancy or current lactation. The ethics committee of Nantes Hospital approved the protocol, and written informed consent was obtained from all the patients.

TREATMENT

Caelyx was administered intravenously once every 4 weeks at a dose of 40 mg/m². Patients received 8 treatment cycles unless the disease was in progression after the 2 first cycles or in complete remission after the fourth cycle. Treatment was also disrupted by the occurrence of a serious adverse event. If progression occurred after the second cycle, the treatment was stopped. If a complete remission was achieved after 2 doses, the patient received 2 additional doses, and if a patient was in complete remission after 4 doses, the treatment was stopped. However, if the patient was not in complete remission after 4 doses, the treatment was continued until 8 doses had been given.

BASELINE AND FOLLOW-UP MEASUREMENT

At baseline each patient underwent a complete physical examination including performance status evaluation. The following clinical findings were recorded: age, sex, histologic type of the CTCL, stage, and pretreatments. The patients were assessed weekly for hematologic toxic effects and monthly for other toxic effects. Treatment effectiveness was assessed monthly.

ASSESSMENT OF RESPONSE

The main end point was the rate of objective response (CR and PR) after treatment. The secondary end points were to evaluate clinical and biological toxic effects of treatment and duration of response and survival. Complete response was defined as the clinical and histologic (when possible) disappearance of all lesions. Partial response was defined as a 50% or greater decrease in the number and size of preexisting lesions. Progression disease (PD) was defined as the appearance of new lesions representing 25% over preexisting lesions, or infiltration of 25% or more of preexisting lesions. Stable disease was defined as any response that did not meet the criteria of CR, PR, or PD. Progression-free survival was defined as the time between the end of treatment and the appearance of a progression. During this time, the patients did not receive any maintenance therapy.

STATISTICAL ANALYSIS

Kaplan-Meier estimates and the log-rank test were used to perform the main efficacy analysis. The log-likelihood ratio test was used to assess different factors. The α risk was set at 5%. All analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).
RESULTS

PATIENTS

Twenty-five patients were enrolled in the study, 14 men and 11 women. Ages ranged from 32 to 77 years (median age, 64 years). The eTable summarizes the clinical data of the 25 patients (available at http://www.archdermatol.com). Ten patients had nontransformed MF; 5 had SS; 5 had histologically transformed SS; and 5 had histologically transformed MF. Most of the patients (15 of 25) had infiltrated plaques (T3). The others were erythrodermic (T4). The TNM status and tumor stages for all patients are listed in eTable. Pretreatments included topical chemotherapy (carmustine and nitrogen mustard), phototherapy (UV-B and psor- alen–UV-A), systemic retinoid, monochemo- therapy (methotrexate, chlorambucil, cyclophosphamide, or etoposide), interferon-alfa, x-ray therapy, extracorpo- real photopheresis, and polychemotherapy (mostly a combination of cyclophosphamide, vincristine, doxorubicin, and prednisone). All pretreatments are summa- rized in the eTable.

Efficacy

The numbers of Caelyx doses, responses to treatment, and outcomes are reported in the eTable. Two patients had only 1 Caelyx dose owing to an anaphylactoid reaction during the first perfusion. Two patients dropped out of the trial after 2 doses owing to progressive disease. One patient died after 3 doses due to renal and hepatic acute insufficiencies not related to treatment. In 1 patient, the treatment was stopped after 4 doses owing to a complete remission. Finally, 2 patients had 5 doses; 2 pa- tients had 6 doses; and 2 patients had 7 doses. The other 13 patients had 8 doses.

At the end of treatment, the response rate was 56% (14 of 25), including 5 CRs and 9 PRs. The CR was de- fined clinically for the 5 patients and was confirmed histologically for 3 of the 5 patients. Nine patients ex- perienced PD during treatment. The overall survival distribution of the 25 patients is shown in Figure 1. The median overall survival time was 43.7 months. Among the 10 patients with SS, 60% had an objective response: 1 CR and 5 PRs. We did not observe any significant difference in response rate according to age (P = .23), sex (P = .90), type of lymphoma (P = .14), histologic trans- formation (P = .20), stage (P = .33), or prior treatment with systemic chemotherapy (P = .88).

Among the 14 patients who experienced an objective response (CR and PR), the median progression-free sur- vival time after the end of treatment was 5 months (Figure 2), and the median overall survival was 45.8 months. Of the 5 patients who achieved CR with Caelyx treatment, 3 experienced relapse after a median of 358 days (60%).

ADVERSE EFFECTS

The main toxic effects are summarized in Table 1. Ad- verse effects rated grade 1 or higher were noted in 80% of the patients (mostly grade 1 and 2, World Health Orga- nization classification). The most frequent adverse events were anemia (36%; n = 9), asthenia (20%; n = 5), nausea and vomiting (20%; n = 5), palmpoplantar erythrodysesthesia (12%; n = 3), neutropenia (12%; n = 3), and stomach pain (12%; n = 3). There was no episode of febrile neutropenia during the treatment. Two grade 4 adverse events were noted and occurred in the same patient: hyperthermia as- sociated with hemophagocytosis. Two patients experi- enced serious infections, in 1 case multiple infections, during treatment. The first patient contracted Staphylococcus aureus septicemia (grade 3) after the third dose of Caelyx. The other patient experienced pneumopathy (grade 3) and a decrease in left ventricular ejection fraction to below 50% (grade 2). Two patients experi- enced serious infections, in 1 case multiple infections, during treatment. The first patient contracted Staphylococcus aureus septicemia (grade 3) after the third dose of Caelyx. The other patient experienced pneumopathy (grade 3) after 4 doses, and 2 episodes of S aureus septicemia (grade 3), 1 after 7 doses and 1 after 8 doses of Caelyx. Neither of these patients experienced neutropenia during treatment nor during the course of the infections.
We report the first prospective multicenter study to our knowledge on pegylated liposomal doxorubicin in the treatment of CTCL. The 25 patients included had CTCL stage IIB to IVB disease recalcitrant to previous treatment. We observed a response rate of 56% (14 of 25) (20% CR [n=5] and 36% PR [n=9]). These results confirm the effectiveness of pegylated liposomal doxorubicin in treating CTCL that was reported in 2 separate studies by Wollina et al.16,17 In the first study, involving 6 patients,16 83% achieved objective response (66% CR and 16% PR); in the second, involving 34 patients,17 88% achieved objective response (44% CR and 44% PR). The response rate was lower in the present study, and there are several possible reasons for the difference. First, patients in our study had more advanced CTCL. The first prior study16 in- cluded 3 patients with stage IB disease (T2N0M0) and 3 patients with stage IIB disease (T3N0-N1M0); the second earlier study17 included mainly patients with T1 to T3 disease (only 2 of 34 patients had T4 status), while 10 of our 25 patients had T4 status. Moreover, none of the patients in the earlier studies16,17 had histologically transformed CTCL; in contrast, 10 of our 25 patients had transformed CTCL.

Second, important differences exist between the patients in our study and those of the earlier studies16,17 in terms of prior therapies. In the first study by Wollina et al.,16 only 1 of 6 patients (16%) had been treated with chemotherapy before undergoing pegylated liposomal doxorubicin treatment. In the second earlier study,17 20% of the patients had undergone prior chemotherapy. In contrast, 60% of our patients had been treated by chemotherapy before receiving Caelyx.

The retrospective study by Di Lorenzo et al.22 of 10 patients with stage IVB MF (T1-T4N0-N3M1) confirms that objective response is poorer in more advanced stage disease. Indeed, these authors observed a 33% partial objective response as opposed to 25% stable disease and 42% PD.

In addition to these few studies assessing the efficacy of pegylated liposomal doxorubicin in the treatment of CTCL, Tsatalas et al.23 reported a long-term complete clinical response to pegylated liposomal doxorubicin in 1 case of resistant tumor-stage MF. Also, Prince et al.24 reported 1 case of stage IB MF and 1 of SS, both previously refractory to intravenous chemotherapy, in which the disease progressed during treatment with pegylated liposomal doxorubicin.

It is important to note that a potential bias might be introduced into our study by prior treatment response and/or treatment refractory disease because most of the patients were not treatment-naı"ve patients. However, it is well known that patients previously treated by other treatments and especially chemotherapies are more difficult to cure.

One interesting point in our study was the efficacy of Caelyx in 2 subgroups of patients with CTCL for whom it had never been studied previously: SS and transformed CTCL. In 10 patients with SS, we observed a high response rate (60%; n=6), including 1 CR (10%; n=1). The median progression-free survival time for responding patients with SS was 2 months. All patients except 1 had been previously treated with at least 2 lines of treatments, including topical carmustine, topical nitrogen mustard, UV therapy, total body electron therapy, radiotherapy, interferon-alfa, retinoids, monochemotherapy, or polychemotherapy. The median number of lines of pre-
treatments was 3, and 70% of the patients with SS had been previously treated by chemotherapy (n = 7).

Patients with transformed CTCL classically have a poor prognosis and low response rates to most therapies.25-27 In these patients, we observed a high response rate (50% of n = 5) including 1 CR (10%). The median progression-free survival time for these patients with transformed CTCL who obtained an objective response with Caelyx was 2 months, and the patient who obtained a CR is still disease free after 3 years.

We observed a higher rate of toxic effects in our study than was reported by Wollina et al,17 which is probably owing to the fact that our study was prospective. In particular, we observed more anemia (36% vs 9%), more asthenia (20% instead of 0%), more nausea and vomiting (20% instead of 3%), and more mucitis (8% instead of 3%). Eighty percent (38 of 47) of the adverse events observed during the treatment were grade 1 or 2; 14% (7 of 47) were grade 3 (1 anemia, 1 asthenia, 3 septicemia, 1 cutaneous ulceration, 1 pneumonia, and 1 auriculoventricular block); and 4% (2 of 47) were grade 4. These results can probably be explained by the difference in doses because the adverse effects with this molecule are known to be dose dependent.28 Wollina et al17 used 20 mg/m² as the dose for 28 patients in their study, 20 to 30 mg/m² for 4 patients, and 40 mg/m² for 2 patients, whereas all of our patients received a dose of 40 mg/m². In our study we observed 4 serious infections (3 cases of S aureus septicemia and 1 pneumonia). These infections are well-known adverse effects of chemotherapy but had never been reported in patients with CTCL receiving pegylated liposomal doxorubicin. These findings emphasize the need for caution when treating patients who have a high risk of infection due to their cutaneous lymphoma. The only patient who experienced a grade 4 adverse effect in our study had an unexplained association of hyperthermia, face edema, and spontaneously regressive hemophagocytosis.

Other chemotherapies tested in advanced or refractory CTCL are listed in Table 2.6,29-52 These treatments are most often used as monochemotherapies. Fludarabine has been used in 4 studies in advanced CTCL,29-32 with an overall response rate of 20% to 51% and a higher response rate when combined with extracorporeal photopheresis (63%).32 Methotrexate has been tested for the same indication in 4 studies.31-36 The best response rates were obtained in erythodermic CTCL (58%33 and 76%34) and the worst ones in T3 disease. Gemicitabine has been evaluated in 2 studies in the treatment of advanced or refractory CTCL and showed response rates of 70%37 and 75%.38 Several studies have suggested the effectiveness of pentostatin in pretreated CTCL with response rates ranging from 33% to over 70%.39-44 Chlorambucil was used in erythodermic CTCL45,46; it was combined with corticosteroids, and the response rate was 100%, with a median duration of response of 12 months in 1 study.46 One study assessing the effectiveness of temozolomide in pretreated stage IIB to stage III CTCL reported a response rate of 33%.47

Polychemotherapy is also frequently used in refractory CTCL. The most common regimens are CHOP containing cyclophosphamide, vincristine, doxorubicin, and prednisone), COP (containing cyclophosphamide, vincristine, and prednisone), and EPOCH (containing etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone). In the very few controlled studies of these polychemotherapy regimens,48-52 the overall response rates range from 40% to 100%.

It is difficult to compare the results of these studies, some of them being prospective and others retrospec-
tive. Moreover, the methods of assessing response were not the same across studies, and the durations of response were not calculated in the same way. For the studies of methotrexate, the time to treatment failure was evaluated starting with the first day of treatment to the failure of the treatment, and the treatment was ongoing. For other studies such as those of gemcitabine, the end point was the time of complete or partial remission after treatment completion. In the studies of Quaglino et al and Akpek et al, the end points were the time to progression defined from the first day of treatment to the progression. For the temozolomide study, the follow-up was very short (6-9 months), explaining the reported short duration of response. And for the oldest studies, the duration of response was not specified.

In summary, the present prospective study demonstrates the effectiveness of pegylated liposomal doxorubicin in treating CTCL, showing a response rate of 53% in refractory, frequently advanced cases. Therefore, pegylated liposomal doxorubicin can be one of the choices in the treatment of CTCL. This treatment was also effective in 2 subpopulations of patients for whom the prognosis is known to be poorer: patients with SS and those with transformed CTCL. Moreover this study shows that if the dose is increased to 40 mg/m², effectiveness is not improved, but toxic effects (especially hematologic) are increased compared with the dose of 20 mg/m².

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Author Contributions: Drs Khammari and Dreno had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Khammari and Dreno. Acquisition of data: Quereux, Marques, Bedane, D’incan, Dereure, Puzenat, Clady, Martin, Joly, Delaunay, Beylot-Barry, Vabres, Celerier, Sasolas, Grange, and Khammari. Analysis and interpretation of data: Quereux, Nguyen, Celerier, and Dreno. Drafting of the manuscript: Quereux. Critical revision of the manuscript for important intellectual content: Quereux, Marques, Nguyen, Bedane, D’incan, Dereure, Puzenat, Clady, Martin, Delaunay, Beylot-Barry, Vabres, Celerier, Sasolas, Grange, Khammari, and Dreno. Statistical analysis: Nguyen.

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Additional Information: The eTable is available at http://www.archdermatol.com.


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<th>Pretreatments</th>
<th>Doses, No.</th>
<th>Patient Response</th>
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<td>T3N0M0</td>
<td>IIIB</td>
<td>TC, UV, retinoid</td>
<td>8</td>
<td>CR</td>
<td>6 mo</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>21/M/72 SS</td>
<td>T4N0M0</td>
<td>III</td>
<td>UV, monoclonal antibodies</td>
<td>6</td>
<td>PD</td>
<td>None</td>
<td>Lost to follow-up</td>
<td></td>
</tr>
<tr>
<td>22/M/48 MF</td>
<td>T3N0M0</td>
<td>IIIB</td>
<td>IFN</td>
<td>8</td>
<td>PR</td>
<td>3 mo</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>23/M/77 MF transformed CD30 +</td>
<td>T3N0M0</td>
<td>IIIB</td>
<td>IFN, TC, retinoid</td>
<td>8</td>
<td>CR</td>
<td>3 y</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>24/M/60 SS transformed CD30 +</td>
<td>T4N3M0</td>
<td>IVA</td>
<td>No previous treatment</td>
<td>8</td>
<td>PR</td>
<td>2 mo</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>25/F/70 MF</td>
<td>T3N0M0</td>
<td>IIIB</td>
<td>TC, UV, monoclonal antibodies</td>
<td>7</td>
<td>PD</td>
<td>None</td>
<td>Dead</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; IFN, interferon; MF, mycosis fungoides; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; SS, Sézary syndrome; TC, topical chemotherapy (topical carmustine or topical nitrogen mustard); UV, phototherapy; XR, x-ray therapy.

a Caelyx is the proprietary name of the patented drug formulation for pegylated liposomal doxorubicin hydrochloride used in the study (Schering-Plough, Kenilworth, New Jersey).

b One dose was 40 mg/m².