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ABSTRACT

Pegylated liposomal doxorubicin (Peg-Doxo) is a promising drug for advanced/recalcitrant primary cutaneous T-cell lymphomas (CTCLs). This prospective phase II trial enrolled 19 patients. We observed overall and complete response rates of 84.2% and 42.1% (with no significant differences between stage I-IIA and IIB-IV patients), and 11% grade III/IV toxicity. After a maximum 46 month-follow-up, median overall (OS), event-free (EFS) and progression-free (PFS) survival were 34, 18 and 19 months. OS, EFS and PFS rates at 46 months were 44%, 30% and 37% respectively. Peg-Doxo seems to be an active and safe principle that should be used in plurirelapsed, early stage-MF and in combination with other chemotherapeutic agents in advanced and aggressive CTCLs.

Key words: pegylated liposomal doxorubicin, primary cutaneous T-cell lymphomas, mycosis fungoides, Sézary syndrome.

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Doxorubicin is an effective agent used in the treatment of non-Hodgkin's lymphoma. However, its therapeutic index is low due to frequent toxicity thus limiting its use. Pegylated liposomal doxorubicin (Peg-Doxo) represents a new chemotherapy delivery system which can improve tolerability and the effectiveness of the anthracycline concentration inside the tumour. Recently, the efficacy and safety of Peg-Doxo have been tested both as single agent and in combination with other cytotoxic agents in a large spectrum of solid tumors and hematological malignancies[1-3] with remarkable results. It has also been used in cutaneous T-cell lymphomas (CTCLs) refractory to prior therapy or in advanced stages, when treatment is particularly unsatisfactory.[4] Experience with Peg-Doxo in this group of patients is encouraging but still limited to studies of single cases of groups of a maximum of 34 patients in the largest series.[5-7] This led therefore to the present prospective study on advanced, relapsed and refractory primary CTCLs using Peg-Doxo as single agent. Results are compared with previous experiences with this drug and other chemotherapeutic options reported in literature.

Design and Methods

Between May 2002 and May 2005, a prospective, multicenter, phase II clinical trial of monochemotherapy with Peg-Doxo was performed in patients with advanced, relapsed and refractory primary CTCLs. The protocol was approved by local ethic committees and all patients gave their written informed consent. Patients aged ≥18 with a performance status (PS)=0-1 according to WHO-ECOG performance score, or aged ≥75 with a 100% PS=0 were included. Patients with other neoplasms, infections, cyclothymic syndromes, autoimmune disorders, hepatic, cardiac, respiratory or renal diseases, allergy to anthracyclines, previous administration of a cumulative anthracycline dose >200 mg/m^2, administration of radio- or chemo-therapy within 4 weeks before starting Peg-Doxo, abnormal blood counts

(i.e. leukocyte <3.0×10⁹/L, platelet <100×10⁹/L and Hb <10 g/dL)) were excluded. Pregnant or lactating women were also excluded and both men and women with reproductive potential were required to use an approved method of contraception.

Pre-treatment evaluation included a comprehensive study of clinical history, physical examination (evaluation, mapping and measurement of skin lesions), and a revision of histological, immunophenotypic and molecular features according to the recently published WHO-EORTC classification scheme.[8] Complete blood cell count, confirmation of any circulating Sézary cells in peripheral blood (PB) smears, routine laboratory tests including renal and liver function, LDH and β2 microglobulin serum levels, thyroid hormones, antinuclear, anti-DNA and anti-thyroid antibodies, PB mononuclear cell immunophenotyping, echocardiogram, a thoraco-abdominal-pelvic CT scan and a bone marrow trephine biopsy were obtained at study entry. TCR-Vβ flow cytometry and PCR for TCRγ and TCRδ were performed on PB specimens from patients with Sézary Syndrome (SS). Disease was staged according to the TNM classification for Mycosis Fungoides (MF), the criteria proposed by the International Society for Cutaneous Lymphoma for SS, and the Ann Arbor classification for CTCLs other than MF.

Peg-Doxo (Caelyx® Schering-Plough) was administered every 4 weeks at the dosage of 20 mg/m² during a 1-hour intravenous infusion, using antiemetic prophylaxis before infusion. Oral pyridoxine 300 mg was administered daily from the beginning of Peg-Doxo treatment until 1 month after its discontinuation to prevent the palmar-plantar erythrodysesthesia (PPE). Blood and urine parameters were monitored before each Peg-Doxo infusion and a complete blood cell count was performed weekly. Physical examination and assessment of skin lesions were carried out before each Peg-Doxo infusion until the end of treatment, and thereafter at one month, at two months, and then every three months.

All patients receiving at least one cycle of Peg-Doxo were considered evaluable for assessment of response and toxicity. Response to treatment was defined as complete remission (CR), very good partial remission (VGPR), partial remission (PR), minor response (mR), stable disease (SD), and progressive disease (PD) according to published criteria.[9] Response was defined after blind assessment by two independent observers, with CR and PR lasting at least 4 weeks. SS response was assessed by the measurement of clinically confirmed disease in the skin and lymph nodes,[9] and on the changes of $CD4^+$ T-cell subsets and clones in PB.[4] Toxicity was carefully monitored and graded by a medical interview, physical examination and laboratory tests.[10] Patients' characteristics and descriptive data were expressed as median and range for continuous variables and by frequency tabulations for categorical variables. Factors affecting achievement of complete remission and progressive disease were assessed using the χ^2 test or Fisher's exact test for contingency tables. Overall survival (OS) was calculated from the time of the enrolment to death or the last follow-up. Event-free survival (EFS) was calculated from the time of the enrolment to any event including death from any causes and PD. Progression-free survival (PFS) was calculated from time of response to PD. Survival curves were plotted using the Kaplan-Meier method. Differences between the curves were assessed using the log-rank test. Statistical significance was set at $p<0.05$.

Results and Discussion

Patients' characteristics are presented in Table 1 (*online appendix*). They showed a median age of 67 yrs., a prevalence of male sex (14 men and 5 women) and II B-IV stage. Most (68%) had MF at various stage, including the folliculotropic variant (23%) and MF transformed into large-cell lymphoma (23%). Sixteen percent of patients had SS and 16% peripheral T-cell lymphoma-unspecified (PTCL–U). All patients had received other therapies before Peg-Doxo. These ranged from topical or oral steroids, PUVA therapy, systemic retinoids, immunotherapy with interferon-α (IFN-α), radiotherapy and various systemic chemotherapy regimens (gemcitabine, daunoxome, chlorambucil, ATRA, fludarabine, mitoxantrone, 2CdA, VNCOP, CHOP, DHAP). One patient also received immunomagnetic purged autologous bone marrow transplantation. MF patients' staging was IB in 2/13 patients, IIA in 2/13, IIB in 5/13, IIIA in 1/13, and IVB in 3/13. PTCL-U patients' staging was Ann Arbor IV. The majority of patients had multiple, generalised skin lesions (79%), 10.5% multiple but localized, 10.5% a single large lesion. Skin lesions were tumors in 47.4% of patients, erythroderma in 21%, patches in 15.8%, and plaques in 15.8%. The median time from initial CTCL diagnosis and the start of Peg-Doxo treatment was 43 months (range 1-252).

Overall, 101 infusions of Peg-Doxo 20 mg/m² were administered. After a median of 6 courses of Peg-Doxo (range 2-8), 8/19 patients achieved a CR (42.1%), 5 patients a VGPR (26.3%) and 3 patients a PR (15.8%). Overall response rate (ORR) was therefore 84.2% (16/19 patients). The median time to the maximal response was 3 months (range 2-8). CR was obtained in 1/4 stage I-IIA compared with 7/15 stage IIB-IV patients. The achievement of a CR was not statistically associated with an earlier stage. These figures are even more prominent if only MF patients are considered, 1/4 stage I-IIA compared with 6/9 stage IIB-IV. CR was also reached in 1/3 SS patients. Three patients (1 MF IIIA, 2 SS) showed no benefit from the treatment. Of these, the MF patient experienced a PD after 2 courses of Peg-Doxo, was then refractory to fludarabine (6 courses) and oral bexarotene, but obtained a VGPR with alemtuzumab. The 2 SS patients showed a SD and a mR after 6 courses of Peg-Doxo,

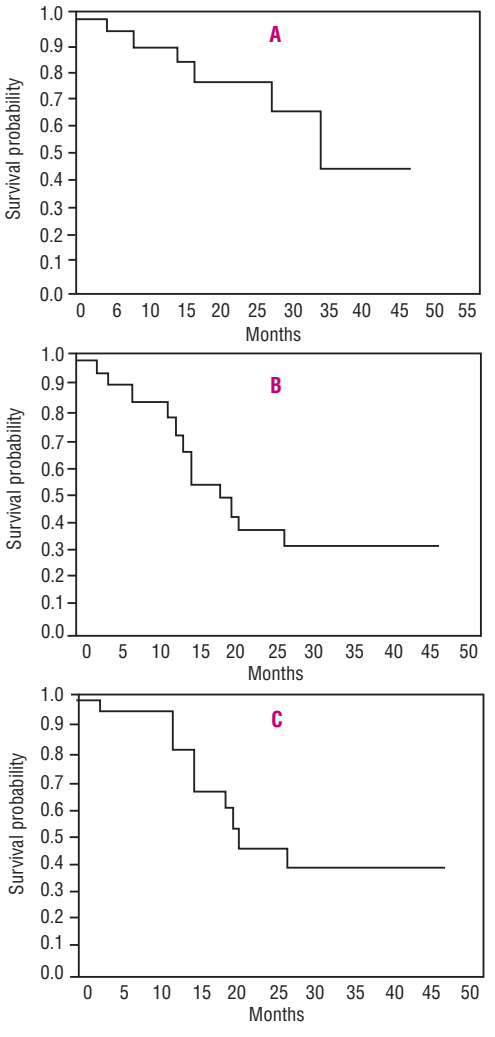

Figure 1. A-C. Results of survival analysis. A. OS curve calculated from time of enrolment to death or the last follow-up. Median OS is 34 months. At 46 months, 44% of patients are still alive. B. EFS curve calculated from time of enrolment to any event, progressive disease and death from any causes or progressive disease. Median EFS is 18 months. At 46 months, 30% of patients are still *event-free*. C. PFS curve calculated from time of the response to major events/progressive disease (PD). Median PFS is 19 months. At 46 months, 37% of patients are still *progression-free*.

were similarly unresponsive to extracorporeal photopheresis (ECP), IFN and fludarabine (6 courses), yet achieved a PR with oral chlorambucil and a VGPR with oral bexarotene respectively. Peg-Doxo monotherapy was successfully tolerated, as overall adverse effects were observed in 5 patients (26%) and grade III-IV toxicity only occurred in 2 patients (11%) *(Table 1, online appendix)*. Therapy was discontinued after 2 courses and not resumed in one patient with PR (voluntary suspension) and in one with VGPR (grade III capillary leakage syndrome). None of the remaining patients decreased or delayed the dose. Hematological toxicity was mild with only one case of grade >II neutropenia, which was successfully treated with granulocyte colony-stimulating factor (G-CSF). No patients experienced neutropenic sepsis, herpes virus or other opportunistic infections. There were no deaths from grade II gastrointestinal toxicity observed in two patients, and grade I PPE in one. After a median follow-up of 22.6 months from enrolment (range 3.4-45.9), 3 patients had only minor events. These were minimal recurrences with limited skin disease responsive to topical steroids. Nine patients had major events/PD. These included 4 PD and 5 significant clinical relapses requiring other systemic therapies. At the last follow-up (September 2005), 12 patients were alive (6 in VGPR/PR and 2 in CR) and 7 dead, 2 for PD and 5 for non-related causes to the disease (case 11, renal carcinoma; case 13, acute myeloid leukaemia; case 15, colonic carcinoma; case 18, pulmonary edema; case 19, pulmonary fibrosis; *Table 1, online appendix*). Median OS, EFS and PFS were 34, 18 and 19 months respectively. OS, EFS and PFS rates at 46 months were 44%, 30% and 37% respectively. (Figures 1 A, B and C). Stage was not found to be significantly associated with PFS. This study confirms previous reports[5-7] which demonstrate that Peg-Doxo is a well tolerated, safe and effective drug in the treatment of advanced and relapsed CTCLs, often refractory to standard therapies. Adverse events were observed in 26% patients, yet grade III-IV in only 11%. We observed CR and OR rates similar to the largest study[7] (42.1% vs 44%, 84.2% vs 88%), but a longer OS and EFS (34 vs 17.8, 18 vs 12 months). This was in spite of the fact that our series included a higher proportion of III-IV stages (53% vs 38%), of SS (16% vs 3%), and PTCL-U (16% vs 6%) cases. Furthermore, a high proportion of patients (79%) had multiple generalised skin lesions. Nodules and erythroderma were present in 47.4% and 21% of patients respectively. In spite of the doubts raised about the efficacy of the drug in patients previously treated by chemotherapy, our series indicates that Peg-Doxo is effective in patients heavily pretreated with chemotherapy. These represented 47% of our cases. It is worth emphasizing that disease stage did not influence either CR or PFS. This was confirmed even when only MF patients were considered, with 6/9 stage IIB-IV achieving a CR.

The clinical benefits of Peg-Doxo in this study are to be considered satisfactory even when compared to the most used and effective regimens.[11-19] However, the reported data have been obtained in different decades and different patient selection and staging criteria have been adopted (*Table 2, online appendix*). The study on BCPE (bleomycin, cyclophosphamide, prednisone and etretinate) reported a higher response rate (CR 85%, OR 90%)[11] and the study on CAVE (endoxan, doxorubicin, etoposide, vincristin) combined with electron-beam irradiation showed a duration of response longer than 12 months combined with a higher OS.[12] But apart from these studies, monochemotherapy with Peg-Doxo seems to be more effective than all the other treatment modalities. like VICOP-B,[13] EPOCH,[15] CVP,[16] CHOP and CHOP-like[17] regimens, and alemtuzumab[14] or gemc-

itabine[18] monotherapy. As far as life expectancy is concerned, it is difficult to verify if Peg-Doxo obtained a real survival benefit by comparing our data to the disease-specific and progression-free survival reported in a large series of 309 MF managed with standard therapy.[19] This study has only a limited number of cases in each disease stage and patient follow-up is much shorter. Therefore, in spite of the encouraging results, additional research is needed to help define the role of Peg-Doxo in the treatment of CTCLs. Given the unsatisfactory grade of recommendation and level of evidence assigned to all chemotherapies for second-line treatment of the stage IIB to IV MF and SS,[4] only appropriate clinical trials on a larger series would allow evidence-based indications for the best therapy to improve therapeutic outcomes in terms of duration of responses and quality of life.

These should compare Peg-Doxo with other agents proven to be effective such as pentostatin or gemcitabine,[18] or design future strategies combining Peg-Doxo with other active drugs. In particular, studies should investigate the use of Peg-Doxo as a debulking therapy before high dose chemotherapy and eventual bone marrow or stem cell transplantation.

Authors' Contributions

SP, SR, NP, PL designed the study; SP, RA, AT, ARS, SM, AS, GB, AG, GM, GR, GF, AB, MS, NN contributed to the acquisition of data; MO and GG performed the statistical analysis; SP,SR,GG,AT analysed the clinical data; GG made the revision of histologic samples; SP,GG,SR,NP wrote the manuscript; SP and GG created the tables and figures.

Conflict of Interest

The authors reported no potential conflicts of interest.

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