Prospective International Multicenter Phase II Trial of Intravenous Pegylated Liposomal Doxorubicin Monochemotherapy in Patients With Stage IIB, IVA, or IVB Advanced Mycosis Fungoides: Final Results From EORTC 21012.

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ORIGINAL REPORT

Prospective International Multicenter Phase II Trial of Intravenous Pegylated Liposomal Doxorubicin Monochemotherapy in Patients With Stage IIB, IVA, or IVB Advanced Mycosis Fungoides: Final Results From EORTC 21012

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ABSTRACT

Purpose
Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma. There is a need for multicenter trials involving defined patient populations using rigorous assessment criteria. We have investigated pegylated liposomal doxorubicin (PLD) in a clearly defined patient population with advanced MF.

Patients and Methods
Eligible patients had stage IIB, IVA, or IVB MF, refractory or recurrent after at least two previous systemic therapies. Patients were registered to receive a maximum of six cycles of PLD 20 mg/m^2 on days 1 and 15, every 28 days (one cycle). The primary end point was response rate (RR).

Results
Nine centers recruited 49 eligible patients. The median number of chemotherapy cycles received was five. There were no grade 3 to 4 hematologic toxicities. Grade 3 or 4 nonhematologic/nonbiochemical toxicities included cardiac symptom (2%), allergy/hypersensitivity (2%), constitutional symptom (4%), hand and foot reaction (2%), other dermatologic toxicity (6%), other GI toxicity (4%), infection (4%), pulmonary embolism (2%), and cardiac ischemia (2%). Of 49 patients, 20 (40.8%) were responders (complete clinical response [CCR] or partial response [PR] as overall response): three (6.1%) experienced CCRs, and 17 (34.7%) experienced PRs. A 50% or greater reduction of cutaneous manifestations was observed in 26 (60.5%) of 43 assessable patients. Two early deaths were reported, resulting from related cardiovascular toxicity and disease progression. The lower limit of the one-sided 90% CI for RR was 31.2%. Median time to progression and median duration of response were 7.4 and 6 months, respectively.

Conclusion
PLD has an acceptable safety profile in patients with advanced MF. The efficacy of PLD seems promising.

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INTRODUCTION

Primary cutaneous T-cell lymphomas (CTCLs) constitute a broad spectrum of disease entities with different clinicopathologic, phenotypic, and molecular features, characterized by a clonal accumulation of T cells in the skin.[1] The incidence of CTCL has increased during the last decades, with a recent estimated incidence of 6.4 new cases per million person-years.[2] The most common subtype is mycosis fungoides (MF), accounting for more than 80% of CTCL cases.[3,4] MF is clinically characterized by long-standing scaly patch lesions usually involving the limb girdle areas and, in a minority, by a slow, progressive evolution over years or even decades from patches to more infiltrated plaques, tumors, erythroderma, and/or visceral involvement.[4]

The therapeutic strategy depends on the stage of disease.[5,6] Indeed, the overall survival (OS) of patients with limited patch- or plaque-stage disease is similar to that of an age- and sex-matched control population, whereas 5-year OS drops down to

approximately 45% in tumor-stage MF and to approximately 20% for patients with nodal involvement.[6-8] Accordingly, treatment options for early-stage disease involve skin-directed therapies such as phototherapy, topical nitrogen mustard, or radiotherapy. For patients with intermediate- or early-stage disease with resistance to skin-directed therapies, biologics such as interferon alfa and the rexinoid bexarotene are used.[9,10] However, the treatment of advanced-stage MF is still a challenge, despite new biologic and targeted therapies and particularly in view of the short duration of response (DOR).[11] Systemic polychemotherapy is widely used.[10] Although response rates (RRs) are high in uncontrolled monocentric studies (from 55% up to 81%),[9] remissions are invariably short lived. The clinical activity of multiagent chemotherapy in terms of both RR and remission duration has not been shown to be superior to single-agent chemotherapy; moreover, multiagent chemotherapy is accompanied by an increased risk of myelosuppression and infection.[9,10]

Pegylated liposomal doxorubicin (PLD) is a new formulation of doxorubicin in which the drug is encapsulated in liposomes and stabilized by the attachment of polyethylene glycol (ie, pegylation) to the liposomal surface, resulting in increased half-life and improved accumulation in tumor tissues.[12-14] Its toxicity profile is characterized by dose-limiting mucosal and cutaneous adverse effects, in particular palmo-plantar erythrodysesthesia syndrome, reported in up to 20% of treated patients.[15,16]

The use of PLD in CTCL has been reported previously, but interpretation of these reports is hampered by the heterogeneity of diagnosis, stage, and dosage applied and/or by the retrospective nature of the studies as well as the lack of rigorous disease assessment criteria. There is an urgent unmet medical need for an effective approach that avoids myelosuppression in patients with advanced disease. Thus, the European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force initiated this trial.

PATIENTS AND METHODS

General Objective and Outline

This was a single-arm phase II study of PLD (Caelyx; Janssen Pharmaceuticals, Beerse, Belgium) in patients with stage IIA, IVA, or IVB advanced MF. After completion of screening investigations, eligible patients were registered to receive PLD as monotherapy intravenously during 1-hour infusions at a dose of 20 mg/m^2 on days 1 and 15, every 28 days (one cycle). A minimum washout period of 2 weeks, during which patients were not allowed to receive any therapy, was required before starting treatment. Treatment started within 5 days of registration. Patients were treated until they received a maximum of six cycles of therapy, reached a maximum cumulative dose of antracyclines of 400 mg/m^2 (including antracyclines from pretreatment), experienced progressive disease or excessive toxicity, or refused further treatment, or until a clinical decision was made to start a new anticancer therapy. Disease was assessed every two cycles until documented progression, and adverse effects of treatment were assessed for each cycle of therapy. Evaluation of the extent of cutaneous involvement with the disease was performed by assessing the tumor burden index (TBI) based on the modified severity-weighted assessment tool[17]; extracutaneous disease assessment was performed by using chest x-ray and abdominal and lymph node ultrasound.

The protocol was approved by the ethics committee of each participating institution, and written informed consent was obtained from every patient. A general outline and CONSORT diagram are provided in Figure 1.

Patient Selection Criteria

Patients eligibility criteria were as follows: histopathologically confirmed diagnosis of stage IIB, IVA1/2, or IVB MF[18]; no CNS involvement or erythroderma (T4); refractory or recurrent disease after two or more previous therapies; no systemic treatment with steroids at the time of study entry; and age $\geq$ 18 years. Prior systemic chemotherapy was allowed if all of the following conditions were met: anthracycline cumulative dose $<$ 200 mg/m^2, no allergy to anthracyclines, and low-dose methotrexate (weekly dose $>$ 30 mg). Patients requiring systemic treatment with steroids for any reason at the time of study entry were excluded. Topical steroid therapy for itch control was allowed, if used before study entry. In addition, patients had to have: ECOG performance status (PS) of 0 to 2; no other prior or concurrent primary malignant tumor (except adequately treated in situ carcinoma of the cervix uteri or squamous or basal cell skin carcinoma); no active infection requiring specific therapy (eg, antibiotics, anti-HIV therapy); left ventricular ejection fraction within normal limits of each institution, measured by echocardiography or by radionuclide angiocardiography; adequate hematologic function (hemoglobin $>$ 10g/dL, WBC $>$ 2 $\times$ 10^9/L, platelets $>$ 75,000/μL, neutrophiles $>$ 1.5 $\times$ 10^9/L); adequate renal and liver functions (serum creatinine and serum bilirubin $\leq$ 1.5$\times$ the upper limit of normal for the institution, AST/ALT $\leq$ 2.5$\times$ the upper limit of normal for the institution). An appropriate method of contraception was necessary.

Written informed consent was obtained before patient inclusion, according to International Conference on Harmonisation/European Union Good Clinical Practice and national and local regulations. The protocol, patient information sheets, and consent forms were translated and approved by all national and regional ethics and research boards in the United Kingdom, Germany, Italy, Switzerland, Austria, and Israel.

End Points and Disease Assessment

The primary end point was overall RR, defined as the proportion of patients responding (complete clinical response [CCR] or partial response [PR; $>$ 50% reduction of skin manifestations]) to treatment as assessed by local investigators. Disease assessment for the primary end point was conducted at baseline, once every 8 weeks during treatment, at the end of protocol treatment, and once every 12 weeks after the end of protocol treatment until disease progression. Disease assessment consisted of cutaneous disease evaluation using an internationally accepted skin scoring system[17,19] for cutaneous involvement (TBI) and the documentation of extracutaneous lesions, as suggested by the consensus response criteria published by Olsen et al.[20] Secondary end points were toxicity of treatment scored according to the Common Terminology Criteria for Adverse Events version 2.0, time to progression (TTP), and duration of response (DOR).

Sample Size and Statistical Method

To determine the success of treatment, a one-step Fleming design was used, with α set at 0.10 and β at 0.05. P_0 was set at 25% and defined as the largest RR that if true implied that the arm did not warrant further investigation. P_1 was set at 45% and defined as the lowest RR that if true implied that the arm did warrant further investigation. Under this hypothesis, the total sample size was calculated to be 48 eligible patients who started treatment. If 15 responses of 48 were obtained, the arm should be further investigated. If more than 48 eligible patients started treatment, the drug should be further investigated when the lower bound of the 90% one-sided CI for RR was $>$ 25% (the RR used in the null hypothesis). All statistical analyses, tables, and listings were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

The study was opened in November 2003 and closed in July 2009. The CONSORT diagram is depicted in Figure 1. In total, 49 patients were registered from six countries and nine centers. All registered patients were eligible and started treatment. The median follow-up time was 10.6 months.

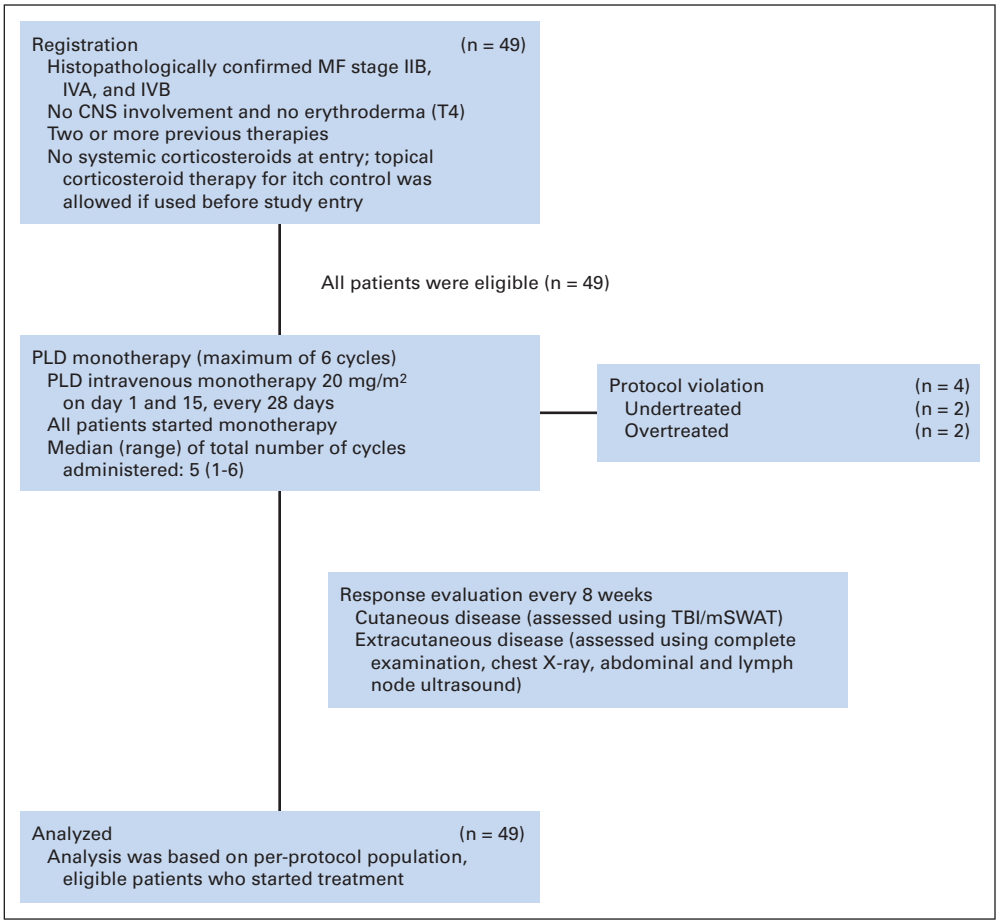

Fig 1. General outline and CONSORT diagram of the EORTC (European Organisation for Research and Treatment of Cancer) 21012 study. MF, mycosis fungoides; mSWAT, modified severity-weighted assessment; PLD, pegylated liposomal doxorubicin; TBI, tumor burden index.

Major demographics and patient characteristics are listed in Table 1. Most patients had a PS of 0 or 1 (96%), had refractory disease (71%), were men (67%), and were between the ages of 56 and 75 years (63%). Prior therapies included combination therapy with or without chemotherapy (22% and 41%, respectively), chemotherapy alone, and topical treatment with or without chemotherapy (14% and 12%, respectively).

The number of cycles of treatment is listed in Appendix Table A1 (online only). The median number of cycles was five (range, one to six), and the median duration of chemotherapy was 20 weeks (range, 4 to 20 weeks). A majority of patients (88%) had relative dose-intensity of 110%. Dose modifications and dose delays were reported in eight (16.3%) and 19 (38.8%) patients, respectively; the main reasons for dose modification or delay were nonhematologic toxicities (48%) followed by patient personal reasons (36%), and hematologic toxicities (9%); the reason was unknown in 7%. Single-cycle dose delays were noted in only 24.5% of patients. Dose interruptions defined as dose skipped or definitely stopped during the cycle were reported in 17 patients (34.7%). Reasons for dose interruptions were nonhematologic toxicities (59%) followed by patient personal reasons (17%) and progression or other medical reasons (12% for each). Of 26 patients with a PS of 1 at baseline, 31% experienced improvement in their condition to a PS of 0, and 23% experienced deterioration of their condition to a PS of 2. Prophylactic antiemetics were administered 88% of patients; 84% had a PS of 0 to 1 during treatment. No patient received granulocyte-macrophage colony-stimulating factor or therapeutic antiemetics.

Toxicity is summarized in Appendix Table A2 (online only). There were no grade 3 to 4 hematologic toxicities; only grade 2 neutropenia (n = 2), leukopenia (n = 2), and anemia (n = 2) were observed during treatment. Grade 3 to 4 nonhematologic or nonbiochemical toxicities included cardiac symptom (n = 1), allergy/hypersensitivity (n = 1), constitutional symptom (n = 2), hand and foot reaction (n = 1), other dermatologic toxicity (n = 3), GI toxicity (n = 2), and infection (n = 2). One patient experienced grade 4 pulmonary embolism, one experienced grade 4 cardiac ischemia, and two experienced grade 3 middle-ear inflammation. Early deaths (death before the first tumor evaluation [ie, within 8 weeks of entering the study]) were reported in two patients; one was the result of related cardiovascular infarction, and the other resulted from disease progression.

RR is summarized in Table 2. Of 49 patients who were eligible and started treatment, 20 (40.8%) were responders: three (6.1%) experienced CCRs, and 17 (34.7%) experienced PRs. The lower limit of the one-sided 95% CI for RR was 31.2%. There was only a minor difference in the efficacy (RR) of therapy in patients with high versus low cutaneous tumor burden (32% *v* 50%; 95% CI, −13% to 49%). Of 36 patients who were chemotherapy naive at registration, 11 (35.5%) were responders, compared with nine responders (50%) of 18 patients who received prior chemotherapy (95% CI, −18% to 47%). Response to treatment in cutaneous disease is shown in Figure

Table 1. Patient Baseline Demographics and Clinical Characteristics (N = 49)

Characteristic	Patients No.	Patients %
Age category, years		
26-35	2	4.1
36-45	1	2.0
46-55	7	14.3
56-65	16	32.7
66-75	15	30.6
> 75	8	16.3
ECOG PS		
0	21	42.9
1	26	53.1
2	2	4.1
Skin patches/plaques		
No	1	2.0
Yes, % BSA		
< 10	8	16.3
≥ 10	40	81.6
Skin tumors		
No	10	20.4
Yes	39	79.6
Clinical lymph node		
No	24	49.0
Yes	25	51.0
Histologic lymph node		
No	34	69.4
Yes	15	30.6
Visceral disease		
No	44	89.8
Yes	5	10.2
Refractory/recurrent disease		
Refractory	35	71.4
Recurrent	14	28.6
Sex		
Male	33	67.3
Female	16	32.7
Prior treatment		
Immunotherapy	3	6.1
Radiotherapy	2	4.1
Chemotherapy	7	14.3
Topical treatment	6	12.2
Combination treatment		
With chemotherapy	11	22.4
Without chemotherapy	20	40.8
Duration from last treatment to trial entry/registration, days		
Median	44.0	
Range	14.0-9,599.0	

Abbreviations: BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Best Response Overall and by Baseline TBI

Best Overall Response to Treatment	Overall (N = 49) No.	Overall (N = 49) %	Baseline TBI* Low (n = 24) No.	Low (n = 24) %	High (n = 25) No.	High (n = 25) %
CCR	3	6.1	3	12.5	0	0.0
PR	17	34.7	9	37.5	8	32.0
SD	14	28.6	7	29.2	7	28.0
PD	5	10.2	1	4.2	4	16.0
Early death						
Toxicity	1	2.0	0	0.0	1	4.0
Other	1	2.0	0	0.0	1	4.0
Not assessable	8	16.3	4	16.7	4	16.0

NOTE. Best overall response (CCR/PR) rate is 40.8%. Exact one-sided 90% CI is 31.2% to 100%.

Abbreviations: CCR, complete clinical response; PD, progressive disease; PR, partial response; SD, stable disease; TBI, tumor burden index.

*Median of baseline TBI = 60 was used as a cutoff point to separate low and high TBI.

2. The waterfall plot depicts the percentage change in patient TBI during treatment relative to baseline TBI. Patients with lymph node and/or visceral involvement (stage IVA/B) had a lower RR than patients with exclusive skin manifestations (stage IIB; 22% *v* 52%; 95% CI, −1% to 60%), as summarized in Appendix Table A3 (online only). In six patients, the response in extracutaneous sites was lower than that in the skin, whereas in most patients, the response in the skin was lower than that in extracutaneous sites.

Secondary end points TTP (defined as the interval of time between the date of registration and the date of first documentation of disease progression) and DOR (measured from the time that measurement criteria were met for CCR/PR [whichever was first recorded] until the first date that recurrent or progressive disease was objectively documented) are shown in Figure 3 and Appendix Figure A1 (online only), respectively. For both TTP and DOR, event was defined as disease progression. Patients who died without progressive disease were censored at the date of death. Patients alive without progressive disease were censored at the last date they were known to be alive. In DOR analysis, only responders (patients with CCR or PR) were included.

Of 49 patients, 35 progressions were observed. The median TTP was 7.4 months (95% CI, 4.5 to 8.6 months). Of 20 responders (CCR/PR), 14 experienced progression. The median DOR was 6 months (95% CI, 5.0 to 10.4 months). At the closure of the study, 14 deaths

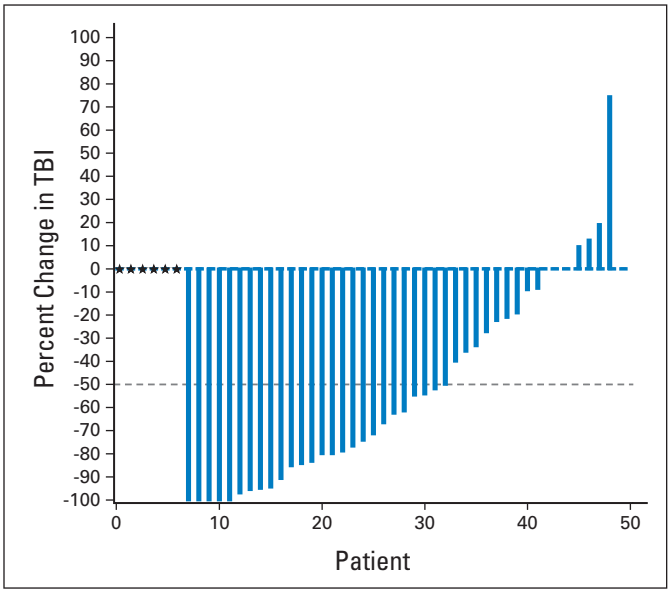

Fig 2. Waterfall plot of the percentage change in tumor burden index (TBI). Star symbols represent patients with nonevaluable TBI.

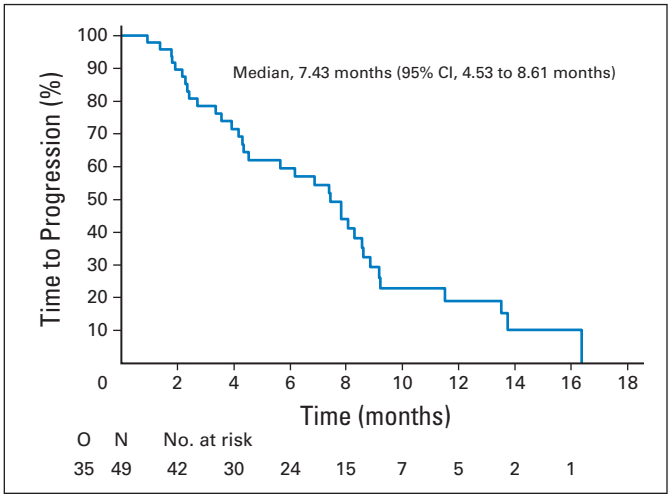

Fig 3. Time to progression. O, observed.

had been observed. Causes of death were disease progression (n = 7), cardiovascular infarction (n = 2), second primary tumor (n = 1), acute perforated gastric ulcer (n = 1), diabetes (n = 1), and infection (n = 2).

DISCUSSION

This trial using PLD in advanced MF is of special interest for the field of CTCL, because it investigates for the first time to our knowledge the outcome of PLD therapy in a clearly defined population of patients with MF urgently in need of cytotoxic therapy. This homogenous population represents the difficult-to-treat elderly patients with MF with disfiguring skin tumors and/or extracutaneous involvement. Most patients had undergone several previous treatments. This is in contrast to many other trials, which are difficult to interpret because of the heterogeneity of diagnosis and varying disease assessments and end points.

The patient population was restricted to a stage of MF with tumors and/or extranodal involvement. Eighty-eight percent of the patients received at least 70% of the planned total dose. PS, age, and pretreatment reflect a realistic population of patients with advanced MF. As shown in Figure 2, with PLD, a substantial improvement in cutaneous lymphoma manifestations was achieved in more than 80% of patients. This was independent from the extracutaneous involvement, which might be explained by a favorable accumulation of the drug in the skin. Because resolution of the disfiguring cutaneous manifestations is crucial to quality of life in this patient population, these cutaneous remissions meet the clinical needs. Moreover, the tolerability of PLD was excellent, without grade 3 to 4 hematologic toxicities or septic complications in a patient population of advanced age; these figures compare favorably with polychemotherapy-associated adverse effects. The overall RR of 40.8% is lower than those reported in other trials using PLD, which have included more heterogeneous populations with regard to stage and diagnosis (Table 3). A reduction in cutaneous manifestations of at least 50% was observed in 26 (60.5%) of 43 assessable patients. Pretreatment with chemotherapy and extent of skin involvement had no negative impact on response, in contrast to extracutaneous involvement (stage IVA/B). As expected, the CCR was low (6%), and the median PFS after discontinuation of therapy calculated from mature data was 7.43 months, highlighting the limitations of chemotherapy and the need for long-term well-tolerated maintenance treatment.[26] Cycling between cytoreductive and maintenance therapies will be the favored therapeutic strategy in the future; it is currently being studied in the ongoing EORTC CTCL protocol.

This is a key report for future therapeutic developments in advanced CTCL. For the first time to our knowledge, RR and DOR in a well-defined population of patients with the most common type of CTCL were determined. There has been one large randomized trial comparing aggressive chemotherapy combined with total skin irradiation with a stepwise adapted mild therapy.[27] However, the major drawback of this trial was the lack of a generally accepted classification at trial initiation, which prevented clear insight into the patient population treated. This drawback applies to many clinical trials performed

Table 3. Summary of Various Prior Studies in CTCL Relative to the Current Study

Variable	Wollina et al[21] (2003)	Di Lorenzo et al[22] (2005)	Pulini et al[23] (2007)	Quereux et al[24] (2008)	EORTC 21012[25]
No. of Patients	34	10	19	25	49
Design	Retrospective multicenter	Retrospective single center	Prospective multicenter	Prospective multicenter	Prospective multicenter controlled
CTCL subtypes and stages	31 MF IB to IVA (n = 31); SS (n = 1); PTCL-U (n = 2); CD30+ ALCL (n = 1)	MF IVB	MF IB to IVB; SS; PTCL-U	MF IIB to IVB (n = 15); SS (n = 10)	MF IIB (n = 31); MF IVA/B (n = 18)
Schedule	20-40 mg/m^2 every 2-4 weeks	20 mg/m^2 every 4 weeks	20 mg/m^2 every 4 weeks	40 mg/m^2 every 4 weeks	20 mg/m^2 every 2 weeks
ORR, %	88.2	30	84.2	56	40.8
CR, %	44.1	0	42.1	20	6.1
Median PFS, months	NA	NA	19	5	6.2
Median OS, months	17.8	NA	34	43.7	NR
Toxicity (grade 3 to 4), %	17.6	10	11	40	20

Abbreviations: ALCL, anaplastic large-cell lymphoma; CR, complete response; CTCL, cutaneous T-cell lymphoma; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PTCL-U, peripheral T-cell lymphoma unspecified; SS, Sezary syndrome.

in the 1980s (summarized by Bunn et al[17]). There have been large registration trials sponsored by the pharmaceutical industries aiming to demonstrate the potency of bexarotene,[28] vorinostat and panobinostat (Duvic et al, submitted for publication),[29,30] and IL-2diphtitox.[31,32] These trials included patients with CTCL of various subtypes and stages to improve recruitment and provide the statistical power to detect beneficial effects if they exist.

Trials investigating the use of PLD in CTCL published earlier included not only MF but Sézary syndrome (SS), unspecified peripheral T-cell lymphomas, and CD30+ anaplastic large-cell lymphomas as well. Some were retrospective patient case collections, which implies a high risk for positive bias. Moreover, two of these studies[21,23] included early-stage MF. These circumstances might explain the higher RRs reported (88.2% and 84.2%, respectively) in comparison with those reported in a French trial[22] and in the trial by Di Lorenzo et al,[24] who included only patients with MF with visceral involvement (56% and 30%, respectively). With regard to drug schedule, the French study anticipated the use of higher dosages (40 mg/m^2) for all patients, whereas the other studies used lower drug doses; the different schedules could explain the significantly higher toxicities (40% grade 3 to 4) experienced in the French study.

The comparison of PLD clinical activity with respect to that of standard mono- or polychemotherapy regimens is difficult. Gemcitabine is a widely used treatment option for MF; however, although its activity is well documented, literature data are difficult to compare. RRs ranged between 62% and 75% according to different reports,[33-35] but inclusion criteria for treatment were different; one study included only untreated patients,[33] whereas another also included those with early-stage MF.[34] Moreover, with respect to the present EORTC study, treated patients included those with erythrodermic MF, SS, and non-MF/SS CTCLs. Regarding adverse effects, the original report by Marchi et al[33] showed a favorable toxicity profile, whereas the French group[35] reported severe hematologic toxicities in 30% of patients, serious infection complications in 26% of patients, and other serious adverse events in 26% of patients, thus contradicting previous studies. One single-institution study reported a 40% RR with a median remission duration of 5.7 months in patients with CTCL treated with COP (cyclophosphamide, vincristine, and prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).[36] Many uncontrolled studies performed in the 1970s and 1980s indicated RRs of 70% or higher with CHOP chemotherapy. However, there is no information on the stage or the precise diagnosis of the patients with CTCL treated,[17] and the remission duration reported did not exceed 6 months in the majority of patient cases.

In summary, this trial has produced benchmark data in a defined population of patients with MF in need of cytotoxic therapy. The efficacy is reasonable, but there is definitely a need for improvement. The inclusion criteria will be used for many additional trials in the CTCL field. The information on PFS after treatment discontinuation provides the setting for new trials of maintenance therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Data analysis and interpretation: Reinhard Dummer, Jürgen C. Becker, Baktiar Hasan, Matthias Karrasch, Sean Whittaker, Martine Bagot
Manuscript writing: All authors
Final approval of manuscript: All authors

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