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Clinical Outcomes of Advanced-Stage Cutaneous Lymphoma under Low-Dose Gemcitabine Treatment: Real-Life Data from the German Cutaneous Lymphoma Network

Christoph Blazejak[a] Rene Stranzenbach[b] Janika Gosman[b] Thilo Gambichler[c] Ulrike Wehkamp[d] Sarja Stendel[d] Claus-Detlev Klemke[e] Marion Wobser[f] Joanna Olk[f] Jan P. Nicolay[g] Maria Weyermann[h] Rudolf Stadler[b] Chalid Assaf[a, i]

[a]Department of Dermatology HELIOS Klinikum Krefeld, Academic Teaching Hospital of the University of Aachen, Aachen, Germany; [b]Universitätsklinik für Dermatologie, Johannes Wesling Klinikum Minden, Minden, Germany; [c]Department of Dermatology, Universitätsklinikum Bochum, Bochum, Germany; [d]Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [e]Department of Dermatology, Städtisches Klinikum Karlsruhe, Akademisches Lehrkrankenhaus der Universität Freiburg, Karlsruhe, Germany; [f]Department of Dermatology, Universitätsklinik Würzburg, Würzburg, Germany; [g]Department of Dermatology Universitätsmedizin Mannheim, Mannheim, Germany; [h]Niederrhein University of Applied Sciences, Faculty of Health Care, Krefeld, Germany; [i]Department of Dermatology, Charité –Universitätsmedizin Berlin, Berlin, Germany

Keywords
Cutaneous T-cell lymphoma · Mycosis fungoides · Sézary syndrome · Peripheral T-cell lymphoma · Blastic plasmacytoid dendritic cell neoplasia · Treatment · Gemcitabine · Chemotherapy · Progression-free survival · Time to next treatment

Abstract

Background: Gemcitabine is an effective single-agent chemotherapy used in advanced stages of cutaneous T-cell lymphoma (CTCL). However, gemcitabine used in the current standard regimen is frequently associated with adverse events (AE), such as an increased risk for myelosuppression and severe infections. ***Objectives:*** We investigated in this retrospective study the effect of low-dose gemcitabine in pretreated advanced-stage CTCL and in blastic plasmacytoid dendritic cell neoplasia (BPDCN) regarding overall response (OR), progression-free survival (PFS), and AE. ***Material and Methods:*** A retrospective, multicenter study was conducted on 64 CTCL and BPDCN patients treated with gemcitabine in average absolute dosage of 1,800 mg/m^2 per cycle, which is 50% lower compared to standard dosage of 3,600 mg/m^2 per cycle (1,200 mg/m^2 day 1, 8, 15). Evaluation of response to therapy and AE was done 4–6 weeks after the sixth cycle. ***Results:*** OR was 62% with 11% demonstrating a complete response. The median time of PFS was 12 months and median time to next treatment was 7 months. Only 3/63 patients showed serious side effects, e.g., port infection or acute renal failure. Almost 73% of the patients experienced

karger@karger.com
www.karger.com/drm

Correspondence to:
Chalid Assaf, chalid.assaf@helios-kliniken.de

Karger

minor to moderate side effects (CTCAE grade 0–2). Fatigue (27.2%), fever (22.7%), and mild blood count alteration (18.2%) were the most common AE. ***Conclusions:*** This retrospective analysis supports the use of low-dose gemcitabine therapy in CTCL, demonstrating with 62% OR and PFS of 12 months an almost identical response rate and survival as compared to the standard dose therapy reported in previous studies but with a significantly improved safety profile and tolerability.

Introduction

Primary cutaneous T-cell lymphoma (CTCL) represents a heterogeneous group of lymphomas that is characterized by a cutaneous infiltration in early stages and a potential systemic distribution of malignant T cells in advanced stages. The 5-year survival rate among patients with CTCL, e.g., mycosis fungoides (MF) in early stage (IA) is 96%, in contrast to patients with extracutaneous disease, where 5-year survival is only 34% [1, 2]. Compared to systemic lymphomas CTCL is a rare disease with a reported increasing incidence of 1 in 100,000 and a median age of 55–60 years [3, 4].

The therapeutic strategy depends primarily on the stage of the disease. In early stages (CTCL ≤IIA), skin-directed therapies as photochemotherapy (PUVA) as a monotherapy or in combination with immunomodulatory agents like interferon-alpha or bexarotene show sufficient clinical response with limited side effects [5]. However, the treatment of advanced CTCL like tumor-stage MF or Sézary syndrome (SS) still poses a challenge. Although first-line treatments often induce clinical responses, remissions are invariably short-lived, thus necessitating more aggressive treatment regimens like cytoreductive drugs, e.g., gemcitabine, doxorubicin, CHOP, and CHOP-like regimen [5]. Since multi-agent chemotherapies have not been shown superior with regard to response rate and duration of remission but are associated with an increased risk of infection and myelosuppression, single-agent chemotherapies are usually preferred [6–8].

Among these single-agent chemotherapies, gemcitabine is frequently used in advanced stages of CTCL. It is effective with high response rates while still having a comparably tolerable side effect profile. It is a nucleoside analog prodrug that works by incorporation into new DNA strands during cell replication. Its toxicity profile is characterized by dose-limiting hematologic side effects and serious infection complications, reported in up to 30% of CTCL patients by the French group [9]. This leads to difficulties in the management of CTCL patients, often directing to premature termination of treatment. This in turn limits the therapeutic response and in addition marks the loss of an effective drug in the limited repertoire of CTCL treatment.

However, the lowest required and effective dosage of gemcitabine chemotherapy has not yet been well evaluated for CTCL patients. As there is still an urgent unmet medical need for an effective approach that avoids myelosuppression in patients with advanced or pretreated cutaneous lymphoma we investigated in this retrospective analysis whether an equally good response with regard to progression-free survival (PFS) and time to next treatment (TTNT) is achievable with lower dose of gemcitabine while showing fewer side effects in patients from German Cutaneous Lymphoma Network.

Patients and Methods

Patient Selection Criteria

Between 2009 and 2019, 64 patients in 7 centers in Germany were treated with a lower than standard dose of gemcitabine (1,200 mg/m^2 at day 1, 8, 15, a total of 6 cycles) [10]. The main inclusion criteria were a histologically proven diagnosis of CTCL/blastic plasmacytoid dendritic cell neoplasia (BPDCN) according to the WHO-EORTC classification system [11] and minimum stage IIB according to the EORTC/ISCL staging system [12]. The study was approved by the Ethics Committee Nordrhein (242/2020) and conducted in accordance with the Declaration of Helsinki.

End Points and Disease Assessment

Disease extent was determined at the time of diagnosis and at the end of treatment with complete physical examination, including complete skin examination and determination of tumor size, laboratory tests, computed tomography (CT) scanning of the chest, abdomen, and pelvis as in the phase II study of gemcitabine as a treatment for the CTCL [10, 12]. CT scanning was repeated at the end of the diagnosis only if they were positive at the time of diagnosis or if there were clinically signs of progression of the disease. Blood test regarding blood involvement of CTCL were done regularly in case of SS and BPDCN according to the standard of care of each center.

Evaluation of therapy response and adverse effects was done 4–6 weeks after the sixth cycle. The therapy response was evaluated by the reduction of skin lesions (e.g., erythema, size, and infiltration) following the ISCL/EORTC criteria by Olsen et al. [12] with complete remission (CR) defined by the complete disappearance of skin lesions, partial remission (PR) defined by reduction of the overall skin involvement >50%, stable disease (SD) with decrease of skin lesions less than 50% in comparison to baseline, and progressive disease (PD) including the response on skin and systemic infiltration (physical examination, CT scan, lymph node sonography) [12, 13].

Table 1. Patient characteristics

	All	BPDCN	MF	pcACLC	PCTCL NOS	SS	*p* value
N (%)	64	4 (6.2)	37 (57.8)	7 (10.9)	5 (7.8)	11 (17.2)	
Sex							
Male, *n* (%)	40 (62.5)	3 (75.0)	24 (64.9)	4 (57.1)	3 (60.0)	6 (54.5)	ns[a]
Female, *n* (%)	24 (37.5)	1 (25.0)	13 (35.1)	3 (42.9)	2 (40.0)	5 (45.5)	
Age at onset							
Median (range)	69 (33–93)	70 (54–75)	69 (46–93)	63 (51–80)	61 (46–89)	67 (33–83)	ns[b]
Mean±SD	66.5±12.1	67.3±9.2	67.0±11.8	65.3±10.7	64.0±17.4	66.3±14.4	
Age at first course of gemcitabine[c]							
Median (range)	73 (36–93)	72 (69–75)	73.5 (50–93)	76 (55–80)	62 (51–89)	73 (36–84)	ns[b]
Mean ± SD	69.6±11.9	72.0±4.2	70.5±11.3	70.1±10.0	65.4±15.9	67.4±15.7	

[a] χ^2 test for differences between groups. [b] Kruskal-Wallis test. [c] Information missing for 8 patients. ns, not significant ($p > 0.05$); SD, standard deviation.

Table 2. Number of previous therapies ($n = 64$ patients)

	All	BPDCN	MF	pcACLC	PCTCL NOS	SS	*p* value
Number of previous therapies							
Median (range)	2.5 (0–6)	0 (0-0)	3 (0–6)	2 (0–4)	2 (0–6)	3 (0–6)	0.40[a]
0	12 (18.8)	4 (100.0)	5 (13.5)	1 (14.3)	1 (20.0)	1 (9.1)	
1	9 (14.1)	–	5 (13.5)	2 (28.6)	1 (20.0)	1 (9.1)	
2	11 (17.2)	–	7 (18.9)	1 (14.3)	2 (40.0)	1 (9.1)	
3	11 (17.2)	–	5 (13.5)	1 (14.3)	–	5 (45.5)	
4	8 (12.5)	–	4 (10.8)	2 (28.6)	–	2 (18.2)	
5	10 (15.6)	–	10 (27.0)	–	–	–	
6	3 (4.7)	–	1 (2.7)	–	1 (20.0)	1 (9.1)	
All	64	4	37	7	5	11	

Data are *n* (%) unless otherwise indicated. [a] Kruskal Wallis test.

Adverse Events

The side effects were evaluated by Common Criteria for Adverse Events (CTCAE) from grade 0 (=none) to grade 4 (=fatal) through regular physical examinations, blood counts, and chemistry profiles. Furthermore, the preceding and following therapies were evaluated.

Statistical Analyses

We first carried out descriptive analyses concerning main patient characteristics as well as diagnoses, therapy (previous therapies and gemcitabine), response, and adverse effects. To investigate potential differences between patients with different diagnoses, associations of patients' characteristics, number of previous therapies, and response rate with diagnoses were assessed by calculating a Mantel-Haenszel χ^2 statistic; if expected cell numbers were <5, Fisher's exact test (two-sided) was used. To compare groups according to age at onset, age at first course of gemcitabine, as well as PFS and TTNT (in case of response) we used Kruskal-Wallis test. All analyses were carried out with the SAS statistical software package (SAS Institute, Inc., SAS Language: Reference. Version 9.4; SAS Institute, Inc., Cary, NC, USA). PFS curves were calculated according to the method of Kaplan and Meier in SPSS 25.

Results

Patient Characteristics

The most common diagnoses were MF (n = 37/64, 58%) and SS (n = 11/64, 17%). Other diagnoses were 7/64 (11%) primary cutaneous anaplastic large cell lymphoma (pcALCL), 4/64 (6%) BPDCN, and 5/64 (8%) primary CTCL not otherwise specified (PCTCL NOS). The median age of onset was 66 years (range 33–93 years), the median age at first treatment with gemcitabine was 70 years (range 36–93 years). 62.5% of the patient were male (n = 40/63) (Table 1).

Table 3. Response rate by diagnoses ($n = 63$ patients), progression-free interval (PFS), and time to next treatment (TTNT) among patients with overall response (ORR) ($n = 41$ patients)

	All	BPDCN	MF	pcACLC	PCTCL NOS	SS	*p* value
Response							
PD	14 (22.2)	1 (25.0)	6 (16.7)	2 (28.6)	1 (20.0)	4 (36.4)	
SD	8 (12.7)	–	5 (13.9)	1 (14.3)	–	2 (18.2)	PD + SD versus
PR	34 (54.0)	2 (50.0)	22 (61.1)	4 (57.1)	2 (40.0)	4 (36.4)	PR + CR: n.s.[a]
CR	7 (11.1)	1 (25.0)	3 (8.3)	–	2 (40.0)	1 (9.1)	
ORR (PR + CR)	41 (65.1)	3 (75.0)	25 (69.4)	4 (57.1)	4 (80.0)	5 (45.5)	
PFS, months[b]							
Median (range)	12 (2–123)	10 (–)	13 (2–123)	14 (11–48)	8.5 (3–13)	6 (2–28)	
Mean ± SD	21.1±26.9	10±(–)	25.7±32.0	21.8±17.6	8.3±4.6	11.2±10.6	
TTNT, months[c]							
Median (range)	7 (0–99)	10 (–)	6 (0–99)	14.5 (2–58)	11.5 (0–27)	6 (5–18)	
Mean ± SD	14.2±19.7	10±(–)	14.2±22.0	22.3±25.2	12.5±14.5	8.8±19.7	
All	64	4	37	7	5	11	

Data are given in column percent (n (%)[col]) unless otherwise indicated. [a] Fisher's exact test for differences between groups; ns, not significant ($p > 0.05$). [b] Information missing for 3 patients. [c] Information missing for 7 patients. SD, standard deviation.

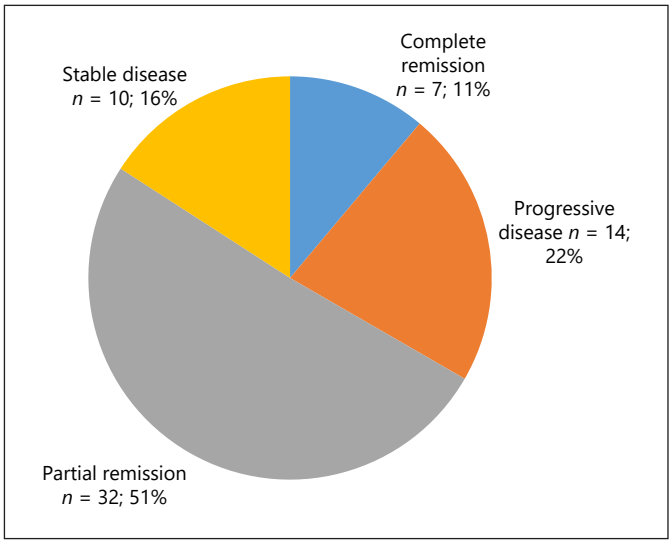

Fig. 1. Response rates of patients with low-dose gemcitabine ($N = 63$).

All patients included were classified with minimum stage IIB according to the WHO-EORTC staging system (8) and for non-MF/SS according to the ISCL/EORTC staging system [14]. 81% ($n = 52/64$) of the patients had received at least one previous therapy (skin-directed, e.g., PUVA or radiotherapy or systemic, e.g., interferon-alpha or bexarotene). The median number of previous therapies was 2.5 (range 0–6) (Table 2).

Gemcitabine dosage administered in all patients was according to the physicians' choice but significantly lower than the standard dosage of 1,200 mg/m^2 day 1, 8, 15, and varied in our patients between 600 mg/m^2 at day 1, 8, 15 per cycle to 1,000 mg/m^2 at day 1 and 15 (designated as "low-dose"). The average absolute dosage was 1,800 mg/m^2 per cycle, which is 50% lower compared to standard dosage of 3,600 mg/m^2 per cycle (1,200 mg/m^2 day 1, 8, 15).

Treatment Results

One case was not evaluated due to a lack of follow-up. The therapy with low dose of gemcitabine showed an ORR (CR + PR) of 65% ($n = 41/63$). A CR was achieved in 11% ($n = 7/63$), a PR in 54% ($n = 34/63$), an SD in 13% ($n = 8/63$). 22% ($n = 14/63$) of the treated patients showed PD (Table 3; Fig. 1, 2). Among the 41 patients with therapy response (ORR) information on PFS and TNT was available among 38 and 34, respectively. The median PFS was 12 months (arithmetic mean: 21.1; range: 2–123) and was comparable to PFS of 10 months found in the phase II study by Marchi et al. [10] (Fig. 3); the median TTNT was 7 months (arithmetic mean: 14.2; range: 0–99).

Adverse Effects

73% ($n = 46/63$) of the treated patients showed no to moderate side effects (no therapy discontinuation or termination, no hospitalization, max. grade 2 CTCAE). 38.1% ($n = 24/63$) of the patients showed no side effects;

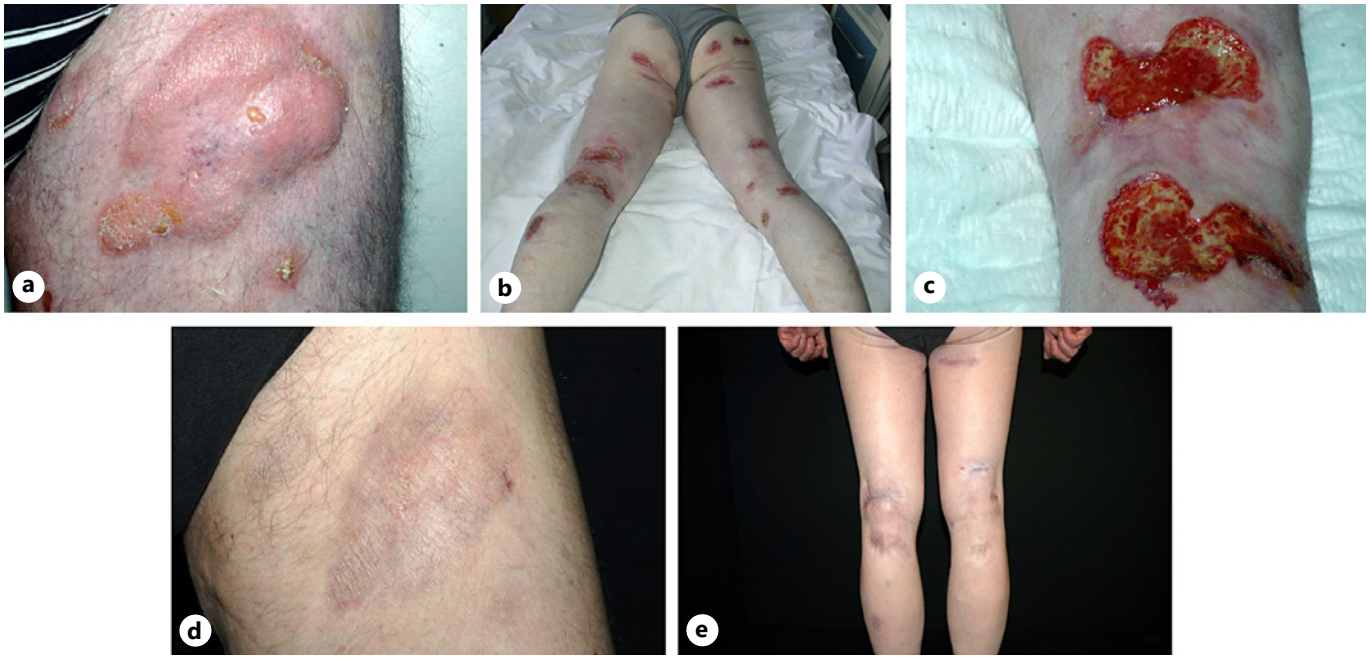

Fig. 2. Patient with MF tumor stage under treatment with low-dose gemcitabine. **a–c** Before treatment with low-dose gemcitabine. **a** Bulky tumor mass on the left thigh. **b** Multiple ulcerated nodules on the back of the legs. **c** Detail. **d**, **e** After 6 cycles of low-dose gemcitabine. **d** Complete remission of the tumor mass on the left thigh. **e** Ulcerated nodules on the back with healing under scar formation.

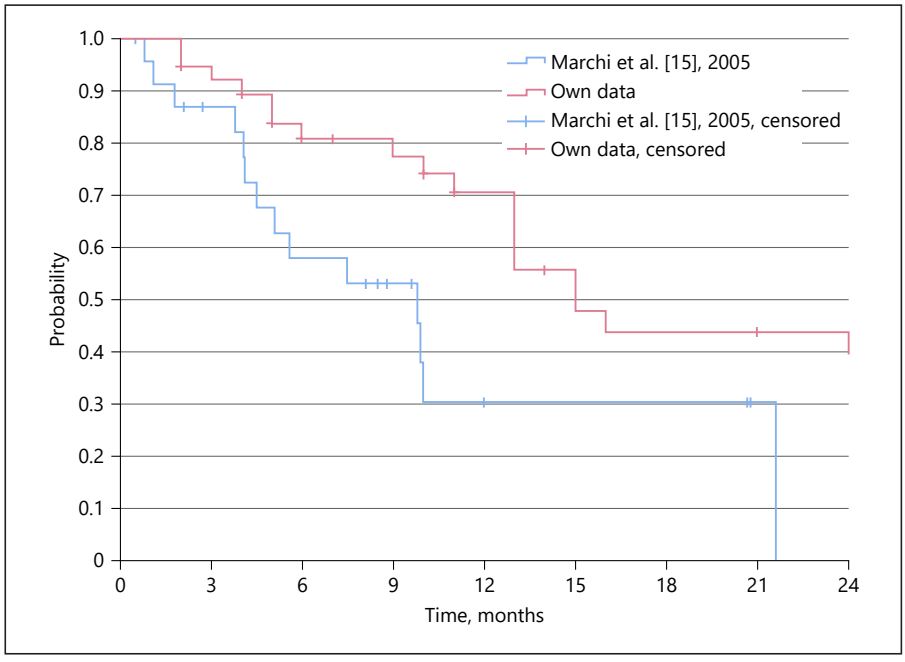

Fig. 3. Progression-free survival of all responding patient of the current study compared to the findings of Marchi et al. [10].

moderate side effects grade 1–2 were seen in 34.9% (n = 22/63). Fatigue (6/22, 27.2%), fever (5/22, 22.7%), and mild blood count alterations (e.g., leukopenia 4/22, 18.2%) were the most common adverse effects (Fig. 4).

17.5% (n = 11/63) of treated patients showed severe side effects like severe blood count alterations (e.g., anemia or leukopenia, 3/11, 27,2%), hepatic (2/11, 18.2%) or renal toxicity (2/11, 18.2%). Fatal adverse effects as

Table 4. Adverse events

	Grade 1–2	Grade 3	Grade 4
Fatigue	6/63 (9.5%)	1/63 (1.6%)	
Fever	5/63 (7.9%)	2/63 (3.2%)	
Leukopenia	4/63 (6.3%)	2/63 (3.2%)	1/63 (1.6%)
Nausea	2/63 (3.2%)		
Renal toxicity		2/63 (3.2%)	
Hepatic toxicity		2/63 (3.2%)	
Pancytopenia	1/63 (1.6%)	5/63 (7.9%)	
Diarrhea	1/63 (1.6%)	1/63 (1.6%)	
Anemia	1/63 (1.6%)	1/63 (1.6%)	
HUS			1/63 (1.6%)
Stomatitis aphthosa		1/63 (1.6%)	
Thrombocytopenia	1/63 (1.6%)		
Sepsis			5/63 (7.9%)

HUS, hemolytic uremic syndrome.

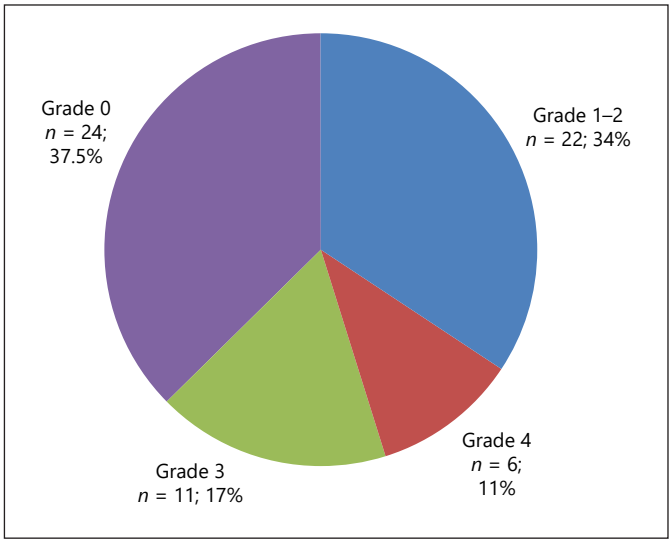

Fig. 4. Adverse events on the low-dose gemcitabine study group.

pancytopenia or sepsis were seen in 11.1% (n = 7/63) (Table 4, 5).

Discussion

Patients with advanced-stage CTCL usually have PD with a high symptom burden. Since available treatments often result in short and incomplete responses, patients are at higher risk of toxicity due to the accumulation of multiple drugs used. Gemcitabine is a single-agent therapy that is easy to administer and relatively well tolerated with a satisfying response rate. It has proven effective in untreated systemic Hodgkin's and non-Hodgkin's lymphomas [15] and in recurrent and refractory systemic lymphomas [16].

In peripheral T-cell lymphomas such as angioimmunoblastic T-cell lymphoma, anaplastic lymphoma, and kinase-negative anaplastic large-cell lymphoma, gemcitabine combined with cisplatin was shown to be effective and not significantly inferior to CHOP [17].

Its effectiveness for CTCL was first demonstrated by Zinzani et al. [18] in 1998 in a phase II study with 13 patients with relapsed or refractory PCTCL NOS or MF with an ORR of 69% and a CR of 8%. After this initial report three major studies with focus on MF and SS followed. Marchi et al. [10] showed in a phase II trial an ORR of 75% and a CR of 22% in 32 untreated patients with CTCL in 2004. In case of therapy response, the PFS was 10 months in median. A further phase II evaluation by Duvic et al. [19] of 31 patients with MF including early stage and 2 patients of pcALCL showed an ORR of 68% and a CR of 8%. The French study group reported in an retrospective analysis an OR of 62.5% and CR in 4% in 16 evaluable patients with only advanced MF/SS in 2009, which is comparable to our study collective. All three studies applied gemcitabine in a dosage of 1,000–1,200 mg/m^2 BS on day 1, 8, 15 of each 28-day cycle (3,000–3,600 mg/cycle) [9, 10, 18, 19].

We present here a retrospective multicenter study treating advanced stage and largely pretreated CTCL patients with a reduced dosage of gemcitabine monotherapy with a total median dosage of 1,800 mg/cycle. Our study, with its considerably large number of patients treated

Table 5. Adverse events of low dose in comparison to normal dose* of gemcitabine – summary of various prior studies in CTCL relative to the current study

Adverse effects	Blazejak et al., 2021 (this article) ($N = 64$)	Marchi et al. [15], 2005* ($N = 32$)	Duvic et al. [16], 2006* ($N = 31$)	Jidar et al. [9], 2009* ($N = 23$)
Grade 3	17.5% (11/63)	28.1% (9/32)	39.4% (13/33)	30% (7/23)[#]
Grade 4	9.5% (6/63)	9.4% (3/32)	6.1% (2/33)	See above

* Normal dosage: 1,200 mg/m^2 day 1, 8, and 15 each 28-day cycle. [#] Defined as grade 3 or 4 (grades not differentiated).

with a low-dose gemcitabine ($n = 64$), demonstrates a comparable ORR of 62% and a CR of 11% (vs. 60–75% and 8–22%, respectively) and a median PFS of 12 months compared to 10 months by Marchi et al. [10], the only previous study where PFS was determined as a secondary endpoint. The medium age in our study of 73 years was higher compared to the previous studies by Marchi et al. [10] (58 years), Duvic et al. [19] (54.8–68 years), and Jidar et al. [9] (64 years). In our study all patients were classified with minimum stage IIB according to the WHO-EORTC and ISCL/EORTC staging system, which is comparable to the previous studies focusing on CTCL [10, 19].

Although the reported studies are therefore not directly comparable due to different study designs (prospective vs. retrospective) and a different patient collective, the high response rates to gemcitabine, even in lower dose as shown in our study, underlines its role as a valuable second-line treatment in advanced or refractory CTCL.

With regard to adverse effects, gemcitabine is known to show a broad range of side effects, from nausea to severe adverse effects (WHO grade 3/4) like pancytopenia or sepsis, which often leads to premature termination of the treatment in CTCL patients [9]. The most frequent WHO grade I/II adverse effects in our study were fever and fatigue (e.g., 9.5% vs. 32%, Duvic et al. [19]) as in the comparative studies. Furthermore, we saw similar severe adverse effects (WHO grade III/IV), however less frequently: leukocytopenia (4.8% vs. 24%, Duvic et al. [19] vs. 16%, Marchi et al. [10]), anemia (1.6% vs. 12%, Duvic et al. [19] vs. 3%, Marchi et al. [10]) or pancytopenia (7.9%, no comparative values), AST/ALT elevations (3.2% vs. 12%, Duvic et al. [19] vs. 6%, Marchi et al. [10]), and sepsis (7.9% vs. 4%, Duvic et al. [19]). Compared to the previous studies, patients treated with low-dose gemcitabine showed comparable or less severe adverse effects: WHO grade III 17.5% in our study versus 39.4% (Duvic et al. [19]), 28.1% (Marchi et al. [10]), or 30% (Jidar et al. [9]) and WHO Grade IV 9.5% versus 6.1% (Duvic et al. [19]), 9.4% (Marchi et al. [10]). Based on the better tolerability of low-dose gemcitabine, all of our investigated patients completed at least six cycles of treatment. This is in contrast to the results of study group by Jidar et al. [9], where only 5/23 patients completed the six cycles; the majority discontinued treatment due to grade 3–4 neutropenia (30%) and complication by severe infections (26%) [9].

The reason for the high efficacy of gemcitabine even at lower dosages has not yet been sufficiently elucidated. However, there are recent data showing that gemcitabine, besides its cytotoxic effects, is also modulating immunologic pathways. In fact, low-dose therapy with gemcitabine has a so-called metronomic effect, which is induced by reduction of T-regulatory cells, therefore leading to an enhanced anti-tumor efficacy [20]. Moreover, metronomic gemcitabine significantly increases apoptosis of cancer-associated fibroblasts, which induce lower expression of pro-angiogenic molecules such as EGF and VEGF and increase the motility of cancer cells and its resistance to chemotherapy [21–23]. The effectiveness of metronomic gemcitabine has been demonstrated clinically in patients with a broad range of malignancies, e.g., bladder carcinomas. Even a dosage of 20% of the regular dosage of gemcitabine showed nearly equal response rates (49.9% vs. 55%) and median time to disease progression (26 vs. 24 months) [24]. Recent studies of low-dose gemcitabine in pancreatic adenocarcinoma patients or for advanced non-small cell lung cancer combined with cisplatin also showed high response rates, whereas interestingly high doses of gemcitabine did not show this effect [25, 26].

In our study, low-dose gemcitabine shows a high response rate and is generally well tolerated. However, based on our retrospective study it is difficult to recommend a certain dosage due to the broad range used in the different centers. The average dosage used in our patient

cohort was 1,800 mg/m^2 as cumulative dosage per cycle distributed on day 1, 8 and 15 or day 1 and 15, demonstrating that the required dosage for a clinical response is much lower than the standard dosage of 3,600 mg/m^2 per cycle (1,200 mg/m^2 day 1, 8 and 15). Besides significantly fewer associated adverse effects as discussed above, the OR and PFS are comparable to the high-dose gemcitabine.

Being a retrospective analysis, this study has limitations due to the heterogenous patient collective and application of not a single fixed dose of the drug. Overall, our retrospective view is in agreement with previous reports showing that gemcitabine is effective in CTCL. In addition, when using gemcitabine in CTCL at lower dose, e.g., only 50% of the standard regimen, gemcitabine is associated with significantly fewer side effects, fewer therapy complications, and fewer therapy interruptions and terminations, which results in this study in a longer therapy response as demonstrated by PFS and TTNT. Additional prospective and randomized studies with low-dose gemcitabine would be valuable to validate these observations.

Conclusions

This study is valuable because it was based on real-life data of advanced-stage and largely pretreated patients with cutaneous lymphoma who were treated in centers of our German Cutaneous Lymphoma Network. Whereas early-stage CTCL has a good prognosis there is a high medical need in this study group. Our treatment outcomes are very encouraging, particularly since we used a markedly reduced dose of gemcitabine. Low-dose gemcitabine was well tolerated and showed good response rates and duration, comparable to other more toxic drugs and drug combinations for this indication with an ORR of 62%, a PFS of 12 months, and a TTNT of 7 months.

Key Message

Low-dose gemcitabine is effective and safe in the treatment of advanced-stage CTCL and BPDCN.

Acknowledgement

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Statement of Ethics

The presented research complies with the guidelines for human studies; the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee Nordrhein (242/2020). Permission to publish the photos was obtained by the patient.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Conceptualization, C.B. and C.A.; data collection, C.B., R.S., J.G., U.W., S.S., C.-D.K., M.W., J.O., J.P.N., and R.S.; writing, C.B. and C.A.; supervision, C.B. and C.A. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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