Journal of Cancer Research and Clinical Oncology (2019) 145:129–136
https://doi.org/10.1007/s00432-018-2772-8

ORIGINAL ARTICLE – CANCER RESEARCH

Trofosfamide in the treatment of elderly or frail patients with diffuse large B-cell lymphoma

Hanno M. Witte[1,2] · Armin Riecke[2] · Thomas Mayer[2] · Tobias Bartscht[1] · Dirk Rades[3] · Hendrik Lehnert[4] · Hartmut Merz[5] · Sebastian Fetscher[6] · Harald Biersack[1] · Niklas Gebauer[1]

Received: 2 June 2018 / Accepted: 11 October 2018 / Published online: 16 October 2018

Abstract

Purpose The introduction of immunochemotherapy has led to a significant improvement in treatment results and prognosis of diffuse large B-cell non-Hodgkins lymphoma (DLBCL) both at initial diagnosis and in relapse. Trofosfamide, an oxazaphosphorine derivative, has been utilized as alternative treatment option for patients with lymphoproliferative diseases unsuitable for conventional chemotherapy agents and protocols because of age, comorbidity, or poor performance score. While data on the activity and safety of single-agent trofosfamide have been published, the potential value of this agent in immunochemotherapy in combination with anti-CD20 antibodies such as rituximab has not been investigated to our knowledge.

Methods Safety and therapeutic effectiveness of trofosfamide given orally at a dose of 50 mg twice daily alone, or in combination with standard-dose rituximab, was investigated in a cohort of elderly and/or highly comorbid patients with histologically confirmed primary or secondary DLBCL.

Results Treatment with trofosfamide in this combination setting was generally well tolerated with no treatment-related deaths and manageable side effects, most of which were WHO class I–II; the most clinically relevant toxicity was cytopenia. 19 of 21 examined patients responded to therapy with 11 of 21 (52.4%) achieving a complete remission (CR). Median overall and progression-free survival (OS and PFS) in the CR-group was 14 and 9 months, respectively. In the subgroup with trofosfamide-based first-line therapy, 7 of 10 (70%) achieved CR and median PFS was not reached.

Conclusions Immunochemotherapy with rituximab and trofosfamide (RT) is safe and effective in elderly and poor-performance patients with DLBCL. Response rates are comparable to most commonly used primary and salvage treatment protocols. The potential value of TR regimen in both first-line and relapsed/refractory DLCBL merits further investigation and is probably underestimated.

Keywords Trofosfamide · Diffuse large B-cell lymphoma · Elderly · Prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL). The incidence of DLBCL closely correlates with increasing age (Swerdlow et al. 2016); median age is 70 years at initial diagnosis. The relationship between age and DLBCL is not only of epidemiological relevance but, more importantly, also of prognostic importance.

Therefore, patient age has been an established adverse prognostic factor in DLBCL both with the use of chemo- and immunochemotherapy. The negative prognostic impact of age is based on a variety of factors: age-related comorbidities may significantly limit treatment tolerance and lead either to undertreatment or to an intolerably high treatment-related morbidity and mortality; moreover, poor tolerance of cytotoxic therapy due to altered renal and hepatic metabolism, reduced organ function, and decreased hematologic reserve may lead to inadequate dosing and intervals and thus to inferior treatment effects.

Harald Biersack and Niklas Gebauer contributed equally to this study.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-018-2772-8) contains supplementary material, which is available to authorized users.

✉ Hanno M. Witte
hanno.witte@student.uni-luebeck.de

Extended author information available on the last page of the article

Despite this, there is undisputed evidence that elderly patients may benefit significantly from age-adjusted therapy regimens, especially since the introduction of rituximab (R) into the therapy of DLBCL (Kouroukis et al. 2002; Peters et al. 2001; Coiffier et al. 2002). This is most evident in patients 80 years and older who are excluded from most prospective trials; despite the potential curability of DLBCL in any age group, the majority of these patients only receive palliative lymphoma therapy (Sehn et al. 2005). Recent phase II studies demonstrate that a dose-adapted combination of rituximab, cyclophosphamide, adriamycin, vincristine and prednisone ("mini-R–CHOP") can result in a 2-year overall and progression-free survival of 59% and 47%, respectively, in octogenarian DLBCL patients (Peyrade et al. 2011).

Unlike the more commonly used oxazaphosphorines such as cyclophosphamide and ifosfamide, trofosfamide is taken orally and continuously. Due to a hepatic first-pass metabolism trofosfamide is transformed into two active metabolites: 4-hydroxy trofosfamide and, to a lesser extent, to 4-hydroxy (4-OH) ifosfamide (Jahnke et al. 2005; Brinker et al. 2002; Potzi et al. 1979; Salminen et al. 1995).

In a variety of reports dating back as far as the 1970s, trofosfamide has been shown to possess antitumor effectiveness in a number of malignancies including soft tissue and bone sarcoma, malignant melanoma, and epithelial tumors such as ovarian carcinoma (Kasper et al. 2005; Reichle et al. 2004; Reichardt et al. 2002; Blomqvist et al. 1995; Gunsilius et al. 2001).

In addition, trofosfamide has been shown to be effective both in Hodgkin's disease and NHL. Its role as an effective single-agent palliative chemotherapy for refractory NHL is primarily derived from a number of phase II trials conducted prior to the introduction of rituximab (Potzi et al. 1979; Salminen et al. 1995, 1997; Wist and Risberg 1991). To the best of our knowledge, the safety and therapeutic effectiveness of trofosfamide-based treatment approaches in DLBCL have not been investigated since the introduction of rituximab in 2001. We, therefore, present a study of patients who received trofosfamide-based therapies either in as first-line or in a setting of relapsed/refractory DLBCL.

Materials and methods

The primary aim of the study was to evaluate the effectiveness of trofosfamide alone or in combination with rituximab in elderly and/or frail DLBCL patients in both in a first-line and a salvage setting. Primary endpoint was overall response rate (ORR), complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) as defined by the International Workshop Criteria (IWSC).

In addition, time to progression (TTP), overall survival (OS) and toxicity profile based on National Cancer Institute Common Toxicity Criteria (NCI CTC; version 2.0) were assessed.

Written informed consent was obtained from all patients and the study was approved by the ethics committee of the University of Luebeck (Reference no. 17-266). The study was completed in accordance with the study protocol.

Patients

All adult (> 18 years) patients with DLBCL diagnosed in accordance with the latest edition of the World Health Organization (WHO) classification of tumors of the lymphoid system (Reference Center for Hematopathology, University of Luebeck) and treated at the University Hospital of Schleswig–Holstein, Luebeck (which provides care to the approximately 1,000,000 inhabitants of southern Schleswig–Holstein, Germany) were identified between January 2010 and July 2017 (Swerdlow et al. 2016). A total of 247 consecutive patients with DLBCL treated with (immuno-)chemotherapy of physician's choice were enrolled in the study. From this cohort, patients who received trofosfamide ($n = 21$), either in front-line or relapsed/refractory setting, were selected for this analysis.

Data concerning performance status [Eastern Cooperative Oncology Group (ECOG)], Charlson comorbidity index (CCI), disease extent, treatment modalities, response rate, relapse pattern, cause of death, and survival were recorded, as were initial serum levels of lactate dehydrogenase (LDH). Staging was performed according to the Cotswold modifications of the Ann Arbor staging system (Lister et al. 1989). The prognostic setting of all DLBCL patients was assessed using the revised international prognostic index (R-IPI) (Sehn et al. 2007). Baseline characteristics of all patients are summarized in Table 1.

Treatment and response

Treatment data were available for all patients and are summarized in Table 2. The choice of treatment was naturally guided by the individual patients risk profile and comorbidities. The latter is summarized for each patient in supplemental table 1 as their extent, as outlined by the CCI, led to the categorization of some relatively young patients as frail and not eligible for more intensive treatment approaches beyond T or TR.

Trofosfamide was administered orally at 100 mg/day continuously in two doses of 50 mg as single-agent therapy (T, $n = 4$) or in combination with rituximab 375 mg i.v. once every 3 weeks (TR, $n = 17$) until progression. Trofosfamide dose did not vary between first-line and relapsed/refractory setting.

Table 1 Baseline and treatment characteristics for all patients included in the study

Characteristics	All patients treated with trofosfamide ($n=21$)	Trofosfamide (+rituximab) in the first-line setting ($n=10$)	Trofosfamide (+rituximab) in the relapsed/refractory setting ($n=11$)
Female	10 (47.6%)	7 (70%)	3 (27.3%)
Male	11 (52.4%)	3 (30%)	8 (72.7%)
Median age (range), years	71.0 (52–91)	86.0 (52–91)	63.0 (52–81)
ECOG performance status (at diagnosis)			
0–2	10 (47.6%)	5 (50%)	5 (45.4%)
3+4	11 (52.4%)	5 (50%)	6 (54.6%)
Ann Arbor stage at diagnosis			
I	2 (9.5%)	1 (10%)	1 (9.1%)
II	4 (19.0%)	1 (10%)	3 (27.3%)
III	6 (28.5%)	4 (40%)	2 (18.2)
IV	9 (43.0%)	4 (40%)	5 (45.4%)
Serum LDH (median)	759 U/l	720 U/l	860 U/l
Extranodal sites			
0–1	12 (57.1%)	6 (60%)	6 (54.6%)
>1	9 (42.9%)	4 (40%)	5 (45.4%)
R-IPI			
0	0 (0%)	0 (0%)	0 (0%)
1–2	8 (38.1%)	4 (40%)	4 (36.4%)
>2	13 (61.9%)	6 (60%)	7 (63.6%)
CNS involvement	2 (9.5%)	2 (20%)	0 (0%)
Best response to trofosfamide (IWSC)			
CR	11 (52.4%)	7 (70%)	4 (36.4%)
PR	6 (28.5%)	1 (10%)	5 (45.4%)
SD	2 (9.5%)	1 (10%)	1 (9.1%)
PD	2 (9.5%)	1 (10%)	1 (9.1%)
Trofosfamide + rituximab	16 (76.2%)	7 (70%)	9 (81.8%)
CCI (median)	12.0	12.0	12.0

ECOG Eastern Cooperative Oncology Group, *LDH* lactate dehydrogenase, *R-IPI* revised international prognostic index, *CNS* central nervous system, *IWSC* International Workshop Criteria, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease, *CCI* Charlson comorbidity index

A rituximab-based first-line therapy was given to all patients who received T or TR in a relapsed or refractory setting (Supplemental table 2).

After achievement of remission, issues of treatment continuation (maintenance therapy) or treatment cessation were discussed with the patients. Treatment was interrupted for 1 week when granulocytopenia or thrombocytopenia of NCI CTC grade 2 occurred. In the rare event of significant non-hematologic toxicity (two cases of acute renal failure in close temporal association with rituximab) of CTC grade 2 or 3, treatment was suspended until symptoms or problems resolved to grade 0 or 1. When treatment with trofosfamide was initiated there was mild hepatic dysfunction in 6 of 21 patients and moderate hepatic dysfunction in 5 of 21 patients with DLBCL. Although trofosfamide metabolism is a primarily hepatic process, known to generate potentially hepatotoxic by-products, we did not detect the onset of any progression of hepatic dysfunction in patients who received trofosfamide. Patients with severe hepatic dysfunction were excluded from trofosfamide-based treatment approaches.

One month after completion of planned treatment, response was assessed in terms of complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) according to the International Workshop Criteria for responding patients (Cheson et al. 1999). Clinical evaluation was performed in a 3-week cycle, which was intensified in the event of suspected therapy-related complications or disease progression.

Statistics

Time to progression (TTP) and overall survival (OS) were calculated from the date of treatment initiation and initial diagnosis, respectively. Survival was estimated by the Kaplan–Meier method; log-rank test was used when comparing groups. All statistical investigations were conducted

Table 2 Treatment characteristics for all patients treated with a trofosfamide-based regimen

Patient no.	Age (years)	Prior lines of therapy	Regimen	Best response[a]	TTP (months)	Last status
1	88	–	Tro (50 mg 1–0–1)	PD	1	Dfd
2	91	–	Tro (50 mg 1–0–1)	SD	5	Dfd
3	86	–	R-Tro (50 mg 1–0–1)	CR	Sus. remission	Alive rem.
4	85	–	R-Tro (100 mg 1–0–1)	CR	Sus. remission	Alive rem.
5	86	–	R-Tro (50 mg 1–0–1)	CR	Sus. remission	Alive rem.
6	78	–	R-Tro (50 mg 1–0–1)	PR	13	Dfd
7	88	–	R-Tro (50 mg 1–0–1)	CR	Sus. remission	Alive rem.
8	87	–	R-Tro (50 mg 1–0–1)	CR	Sus. remission	Alive rem.
9	52	–	R-Tro (100 mg 1–0–1)	CR	Sus. remission	Alive rem.
10	71	–	Tro (50 mg 1–0–1)	CR	Sus. remission	Alive rem.
11	59	2	R-Tro (50 mg 1–0–1)	PR	6	Dfd
12	81	1	R-Tro (100 mg 1–0–1)	CR	Sus. remission	Alive rem.
13	65	3	R-Tro (50 mg 1–0–1)	CR	Sus. remission	Alive rem.
14	62	2	R-Tro (50 mg 1–0–1)	SD	2	Dfd
15	68	2	R-Tro (50 mg 1–0–1)	PR	4	Dfd
16	57	2	Tro (50 mg 1–0–1)	PR	5	Dfd
17	52	2	R-Tro (50 mg 1–0–1)	PR	6	Dfd
18	71	3	R-Tro (50 mg 1–0–1)	PD	1	Dfd
19	63	3	R-Tro (50 mg 1–0–1)	PR	3	Dfd
20	56	2	R-Tro (50 mg 1–0–1)	CR	Sus. remission	Alive rem.
21	68	2	R-Tro (50 mg 1–0–1)	CR	Sus. remission	Alive rem.

TTP time to progression during trofosfamide-based treatment, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease, *Tro* trofosfamide, *Sus. remission* sustained remission, *Dfd* died from disease, *Alive rem.* alive and in remission

[a]During trofosfamide-based treatment

using GraphPad PRISM 6. We performed an independent subgroup analysis for patients receiving trofosfamide-based (with or without rituximab) first-line therapies as well as those who were treated with trofosfamide in the salvage setting.

Patient characteristics

Twenty-one of 247 evaluable DLBCL patients (8.5%; 11 men and 10 women, median age 71.0, range, 52–91 years) received trofosfamide either in the front-line setting ($n = 10$) or in the relapsed/refractory setting ($n = 11$) and were included in the current study. Eleven of the 21 patients were older than 70 years of age.

In the group of patients receiving trofosfamide-based salvage therapy, in median 2.1 prior lines of therapy (range 1–3) had been given. Most patients developed early relapse following prior chemotherapy with only a few cases of primary or secondary refractory disease (data not shown). Median time to progression following prior lines of therapy was 14.3 months. The median Charlson comorbidity index (CCI) was 12.0 points in the overall study population. CCI was 12 points in the RT-first-line group and also 12.0 points in the RT-relapsed/refractory group. Ten patients were under 70 years of age; median CCI in this group was 11.2 points.

Patients were treated with trofosfamide if they were not eligible for R–CHOP or other alternative therapies because of comorbidities and age or because there were no other treatment options available.

Histolopathology

Via the algorithm by Hans et al. (2004), immunophenotypic analysis identified 8/21 germinal center-derived lymphomas (GCB type) and 8/21 activated B-cell lymphomas (ABC type) in the study group. Solely, one case in the group of ABC-type lymphomas was associated with Epstein–Barr virus (EBV) infection (1/8) while the remaining cases tested negative for EBV-encoded small RNAs (EBER chromogenic in situ hybridization). Simultaneous secondary transformations of indolent lymphomas at diagnosis (ssDLBCL) with composite histology and a significant concurrent fraction of follicular lymphoma were found in 4/21 cases. As expected, these cases presented with a germinal center-derived immunophenotype. One case presented as a primary CNS lymphoma with a non-GCB phenotype. Histopathological findings for patients being treated with trofosfamide in first-line

therapy compared with those who were treated trofosfamide-based in refractory/relapsed setting are summarized in supplemental table 2.

FISH studies were performed sporadically in only four cases of GCB-Type DLBCL. Genetic aberrations for cMYC could be detected in none of these cases. All ssDLBCLs in this study were positive for BCL2 translocation due to prior history of follicular lymphoma. Chromosomal translocations for BCL6 were not investigated as part of routine diagnostics.

Treatment and toxicity

The toxicity profile was mild and predominantly hematological in nature with only one case of grade 3 NCI CTC granulocytopenia and subsequent neutropenic infection (pneumonia). Other toxicities included grade 3 gastrointestinal mucositis in one patient and grade 2 acute renal failure in two patients. Renal dysfunction was most likely caused by treatment-associated tumor lysis syndrome. This complication has been reported following treatment of DLBCL with rituximab (http://www.accessdata.fda.gov 02 April 2018).

Outcome and effectiveness

At a median follow-up of 14.0 months (mean 29.0 months; range 1–157 months), 15 of 21 patients (68.2%) had experienced relapse after initial treatment. In the group of patients treated with trofosfamide-based first-line therapy, relapse was observed in three of ten patients at a median follow-up of 11.5 months (range 1–96 months). Median post-relapse survival was 4 months (range 0–14 months) in the RT group and 2 months (range 0–4) in patients who received T as first-line therapy.

Of 21 patients receiving trofosfamide, 19 responded to therapy and 11 (52.4%) achieved CR with a median overall survival (OS) of 14 months and progression-free survival (PFS) of 9 months. In patients receiving trofosfamide-based first-line therapy, 7 out of 10 (70%) achieved CR with median PFS not reached (Fig. 1). All patients who achieved CR during the course of trofosfamide therapy remained event free during the observation period.

There was no significant difference in overall survival between patients who received T or RT as first-line therapy and those were treated in a relapse setting.

Discussion

DLBCL treatment in elderly and/or frail patients poses a challenge to the clinician as there are limited data on the effectiveness and tolerability of established curative regimens initially devised for a young and generally healthy patient population.

Numerous agents have been investigated in phase II clinical trials, yet no standard of care for DLBCL patients ineligible for standard-dose regimens such as R–CHOP, mini-R–CHOP or R–Bendamustine has emerged so far. Based on the Charlson comorbidity index (CCI), the study cohort showed a significant number of comorbidities, which limit the applicability of standard-dose chemotherapy both in the front-line as was as in the relapse/refractory setting.

We show that the combination of rituximab and trofosfamide is a safe and effective strategy for elderly patients or those who for reasons other than age present with a significantly elevated risk for therapy-related morbidity and mortality in the context of standard chemotherapy and immunochemotherapy of DLBCL. In addition, we demonstrate these effects can be realized not only in first-line setting but also in patients with relapsed or refractory DLBCL.

A total of 19/21 patients (90.5%) experienced disease control up to complete remission with T or TR at the first

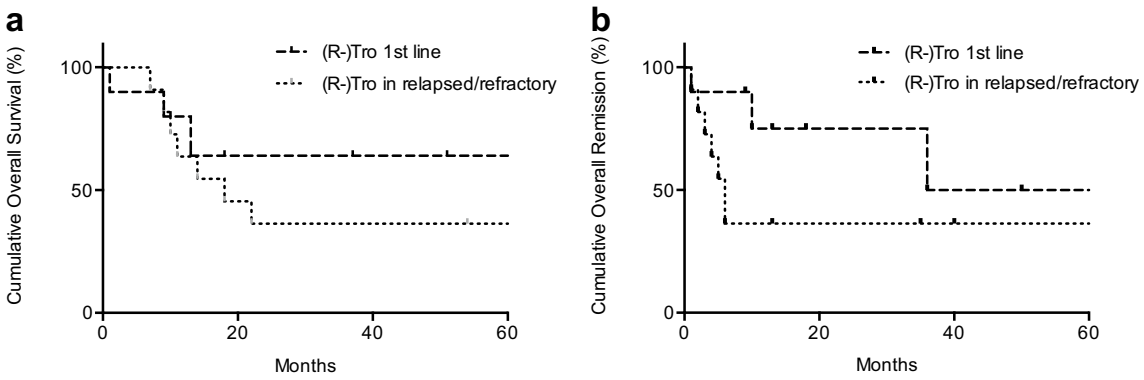

Fig. 1 Kaplan–Meier survival curves. **a** Cumulative overall survival (OS). **b** Cumulative overall remission (progression-free survival) for patients receiving trofosfamide alone or in combination with rituximab in the first-line setting ((R-)Tro 1st line) and patients treated with trofosfamide alone or in combination with rituximab in the relapsed/refractory setting ((R-)Tro in relapsed/refractory)

response assessment. In accordance with the data from trials using trofosfamide for patients with a single-agent therapy for Hodgkin's lymphoma, ovarian cancer, and soft tissue sarcoma, the T was well tolerated in combination with rituximab. The vast majority of cycles could be given without dose reductions or delays.

Dose-adjusted R-CHOP ("mini R–CHOP") protocols or the combination of rituximab and bendamustine (BR) are currently the most commonly chosen treatment regimens for elderly and frail DLBCL patients (Ohmachi et al. 2013; Park et al. 2016; Pfreundschuh 2010). The question what treatment intensity should be recommended in the context of an elderly or fail patient's individual circumstances remains at the discretion of the treating physician and is, therefore, not easily amenable to pragmatic algorithms; moreover, treatment-related decisions in this particular patient population can only be made, tailored and justified by carefully discussing the individual risk–benefit ratio of a planned curative lymphoma therapy with the patients.

Despite the shortcomings of this study (retrospective design, limited size of the study group), the results especially among patients receiving trofosfamide-based induction therapy presented are comparable to most currently used regimens for this specific patient population with regards to PFS and OS, and may be superior with regard to treatment toxicity and tolerability. This is especially relevant as dose reductions in R–CHOP and similar regimens have been demonstrated to significantly diminish treatment effectiveness (Kanemasa et al. 2017). Another significant beneficial aspect of T and RT lies in the continuous oral application which increases patient independence and results in an extremely low hospitalization rate in our cohort (10%). Worth mentioning at this point is that the initial treatment for patients who were treated with T or TR in relapsed or refractory setting included rituximab in all cases. Regarding the circumstance that these patients were not rituximab naive upon treatment initiation with trofosfamide, the described therapeutic effectiveness is most likely not attributable to the anti-CD20 therapy.

Trofosfamide is an oxazaphosphorine that is rarely included in cytoreductive treatments despite pharmacokinetic advantages over the most commonly used drug of this group (cyclophosphamide), such as better enteral absorption and improved lipid solubility. The prodrug is hepatically activated through the generation of 4-hydroxy metabolites, which are partly identical with derivatives of cyclophosphamide and ifosfamide (Hempel et al. 1997; Zhang et al. 2005).

The metabolite 4-hydroxytrofosfamide, however, is of special interest in lymphoma therapy as it is a metabolization product exclusive to trofosfamide which has been shown to penetrate the central nervous system (CNS) far more effectively than cyclophosphamide or ifosfamide derivatives, potentially explaining the fact that we could document high CNS response rates and the absence of CNS relapse despite high risk for CNS dissemination in many of our patients (Boos et al. 1993). Further studies should be conducted to investigate the effectiveness of this treatment option for primary DLBCL of the CNS.

The continuous application of trofosfamide has the significant advantage of even drug levels over time which targets cells with limited periods of drug susceptibility as opposed to higher doses of chemotherapy in a block-type regimen which only affects the susceptible fraction of tumor cells during a limited timeframe. As we avoided high and toxic drug levels, the applicability of trofosfamide was optimized for our cohort of elderly patients with abundant comorbidities (median CCI: 12.0 points) (Wolff et al. 2000).

As retrospective study with a limited patient number shortcomings, some have to be mentioned in this discussion. For example, some patients ($n = 3$) received dose-intensified therapy (200 mg/day) at the physician's discretion that differed from the standard study dose (100 mg/day); moreover, the intervals of rituximab applications were standardized in some cases ($n = 4$). Furthermore, the duration of treatment continuation once CR was achieved was not standardized. Last, the possibility of a selection bias cannot be ruled out by our study design. These data must, therefore, be reproduced, corroborated or modified by larger and more rigidly standardized study protocols. However, the heterogenous nature of DLBCL disease biology and non-hematological comorbidity may limit the possibilities of this approach in frail and elderly patients.

A significant difference between low-dose trofosfamide maintenance and treatment suspension once complete remission was achieved could not be observed (data not shown). This issue could only be clarified by investigating a much larger study population.

In summery, trofosfamide is a highly cost-effective treatment option for elderly and/or frail DLBCL patients, and provides a high degree of therapeutical effectiveness at a fraction of the cost of other regimens and drugs currently explored in the same setting (e.g. lenalidomide) (Reissig and Walther 2013).

Our results highlight the need not only for a prospective evaluation of rituximab and trofosfamide in elderly or frail DLBCL patients in comparison with established regimens but also for more refined tools to define the optimal treatment intensity in these patients. Clinical decision-making in this very demanding and deserving patient population could significantly benefit from this research in first-line and relapse, and in palliative as well as in the curative setting.

Acknowledgements The authors would like to thank Svenja Kopelke and Rudina Marx for their administrative support.

Author contributions Study design and drafting of manuscript: NG, HW, HB and DR. Data collection and analysis, revision of manuscript: HW, NG, HL, HM and SF. Revision and final approval of manuscript: all authors.

Funding The authors declare no funding source for this study.

Compliance with ethical standards

Ethical approval This study was approved by the ethics committee of the University of Luebeck (Reference no: 17-266) and was conducted in accordance with the Declaration of Helsinki and internationally accepted ethical guidelines.

Informed consent Upon hospital admission, all participants gave their written informed consent for the storage of personal data and the use of data for research purposes.

Availability of data and materials Data supporting the conclusions of this article are included in the article.

Conflict of interest The authors declare that they have no conflict of interest.

References

Blomqvist C, Wiklund T, Pajunen M, Virolainen M, Elomaa I (1995) Oral trofosfamide: an active drug in the treatment of soft-tissue sarcoma. Cancer Chemother Pharmacol 36:263–265

Boos J, Kupker F, Blaschke G, Jurgens H (1993) Trofosfamide metabolism in different species-ifosfamide is the predominant metabolite. Cancer Chemother Pharmacol 33:71–76

Brinker A, Kisro J, Letsch C, Bruggemann SK, Wagner T (2002) New insights into the clinical pharmacokinetics of trofosfamide. Int J Clin Pharmacol Ther 40:376–381

Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-Lopez A, Hagenbeek A et al (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol **17**:1244

Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P et al (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235–242

Gunsilius E, Gierlich T, Mross K, Gastl G, Unger C (2001) Palliative chemotherapy in pretreated patients with advanced cancer: oral trofosfamide is effective in ovarian carcinoma. Cancer Invest 19:808–811

Hans CP, Weisenburger DD, Greiner TC et al (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103:275–282

Hempel G, Krumpelmann S, May-Manke A, Hohenlochter B, Blaschke G, Jurgens H, Boos J (1997) Pharmacokinetics of trofosfamide and its dechloroethylated metabolites. Cancer Chemother Pharmacol 40:45–50

Jahnke K, Wagner T, Bechrakis NE, Willerding G, Coupland SE, Fischer L, Thiel E, Korfel A (2005) Pharmacokinetics and efficacy of ifosfamide or trofosfamide in patients with intraocular lymphoma. Ann Oncol 16:1974–1978

Kanemasa Y, Shimoyama T, Sasaki Y, Tamura M, Sawada T, Omuro Y, Hishima T, Maeda Y (2017) The impacts of initial and relative dose intensity of R-CHOP on outcomes of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 58:736–739

Kasper B, Ho AD, Egerer G (2005) A new therapeutic approach in patients with advanced sarcoma. Int J Clin Oncol 10:438–440

Kouroukis CT, Browman GP, Esmail R, Meyer RM (2002) Chemotherapy for older patients with newly diagnosed, advanced-stage, aggressive-histology non-Hodgkin lymphoma: a systematic review. Ann Intern Med 136:144–152

Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, Rosenberg SA, Coltman CA, Tubiana M (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 7:1630–1636

Ohmachi K, Niitsu N, Uchida T, Kim SJ, Ando K, Takahashi N, Takahashi N, Uike N, Eom HS, Chae YS et al (2013) Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 31:2103–2109

Park SI, Grover NS, Olajide O, Asch AS, Wall JG, Richards KL, Sobol AL, Deal AM, Ivanova A, Foster MC et al (2016) A phase II trial of bendamustine in combination with rituximab in older patients with previously untreated diffuse large B-cell lymphoma. Br J Haematol 175:281–289

Peters FP, Fickers MM, Erdkamp FL, Wals J, Wils JA, Schouten HC (2001) The effect of optimal treatment on elderly patients with aggressive non-Hodgkin's lymphoma: more patients treated with unaffected response rates. Ann Hematol 80:406–410

Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S, Coiffier B, Haioun C, Bologna S, Fitoussi O et al (2011) Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 12:460–468

Pfreundschuh M (2010) How I treat elderly patients with diffuse large B-cell lymphoma. Blood 116:5103–5110

Potzi P, Aiginger P, Kuhbock J (1979) [Ixoten therapy in malignant lymphomas]. Acta Med Austriaca 6:247–249

Reichardt P, Pink D, Tilgner J, Kretzschmar A, Thuss-Patience PC, Dorken B (2002) Oral trofosfamide: an active and well-tolerated maintenance therapy for adult patients with advanced bone and soft tissue sarcomas. Results of a retrospective analysis. Onkologie 25:541–546

Reichle A, Bross K, Vogt T, Bataille F, Wild P, Berand A, Krause SW, Andreesen R (2004) Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. Cancer 101:2247–2256

Reissig A, Walther M (2013) Old wine in new pipes? Treatment of advanced non-small cell lung cancer with trofosfamide. Onkologie 36:409–413

Rituximab Package Insert. Biogen Idec Inc., and Genentech, Inc. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103705s5344lbl.pdf. Accessed 02 Apr 2018

Salminen E, Nikkanen V, Lindholm L (1995) Trofosfamide is effective in refractory non-Hodgkin's lymphoma. Eur J Cancer 31A:2419–2420

Salminen E, Nikkanen V, Lindholm L (1997) Palliative chemotherapy in non-Hodgkin's lymphoma. Oncology 54:108–111

Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, MacPherson N, O'Reilly S, Spinelli JJ, Sutherland J et al (2005) Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 23:5027–5033

Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, Klasa R, Savage KJ, Shenkier T, Sutherland J et al (2007) The

revised International prognostic index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 109:1857–1861

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127:2375–2390

Wist E, Risberg T (1991) Trofosfamide in non-Hodgkin's lymphoma. A phase II study. Acta Oncol 30:819–821

Wolff JE, Molenkamp G, Westphal S, Pietsch T, Gnekow A, Kortmann RD, Kuehl J (2000) Oral trofosfamide and etoposide in pediatric patients with glioblastoma multiforme. Cancer 89:2131–2137

Zhang J, Tian Q, Yung Chan S, Chuen Li S, Zhou S, Duan W, Zhu YZ (2005) Metabolism and transport of oxazaphosphorines and the clinical implications. Drug Metab Rev 37:611–703

Affiliations

Hanno M. Witte[1,2] · Armin Riecke[2] · Thomas Mayer[2] · Tobias Bartscht[1] · Dirk Rades[3] · Hendrik Lehnert[4] · Hartmut Merz[5] · Sebastian Fetscher[6] · Harald Biersack[1] · Niklas Gebauer[1]

Armin Riecke
arminriecke@bundeswehr.org

Thomas Mayer
thomas5mayer@bundeswehr.org

Tobias Bartscht
tobias.bartscht@uksh.de

Dirk Rades
dirk.rades@uksh.de

Hendrik Lehnert
hendrik.lehnert@uksh.de

Hartmut Merz
merz@haematopathologie-luebeck.de

Sebastian Fetscher
sebastian.fetscher@sana.de

Harald Biersack
harald.biersack@uksh.de

Niklas Gebauer
niklas.gebauer@uksh.de

[1] Department of Haematology and Oncology, University Hospital of Schleswig-Holstein (UKSH), Ratzeburger Allee 160, 23538 Lübeck, Germany

[2] Department of Haematology and Oncology, German Armed Forces Hospital Ulm, Oberer Eselsberg 40, 89081 Ulm, Germany

[3] Department of Radiation Oncology, University Hospital of Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany

[4] Department of Internal Medicine I, University Hospital of Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany

[5] Reference Center for Lymph Node Pathology and Haematopathology, Lübeck, Germany

[6] Department of Haematology and Oncology, Sana Hospitals, Lübeck, Germany