Journal of Cancer Research and Clinical Oncology (2019) 145:3067–3073
https://doi.org/10.1007/s00432-019-03027-6

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Modified DHAP regimen in the salvage treatment of refractory or relapsed lymphomas

Frank Kroschinsky[1] · Denise Röllig[1] · Barbara Riemer[1] · Michael Kramer[1] · Rainer Ordemann[1] · Johannes Schetelig[1] · Martin Bornhäuser[1] · Gerhard Ehninger[1] · Mathias Hänel[2]

Received: 6 June 2019 / Accepted: 16 September 2019 / Published online: 28 September 2019

Abstract

Background The combination of dexamethasone, high-dose cytarabine, and cisplatin (DHAP) is an established salvage regimen for lymphoma patients. We hypothesized that a modified administration schedule for cisplatin and cytarabine results in lower toxicity and improved efficacy.

Methods We retrospectively analysed 119 patients with relapsed or refractory, aggressive, or indolent B-cell lymphomas, mantle-cell lymphomas, peripheral T-cell lymphomas, or Hodgkin's lymphomas who were treated with the modified DHAP (mDHAP) regimen (dexamethasone 40 mg 15 min-i.v. infusion, days 1–4; cytarabine 2×0.5 g/m^2 1 h-i.v. infusion, days 1–4; cisplatin 25 mg/m^2 24 h-i.v. infusion, days 1–4). Responding and eligible patients underwent stem-cell transplantation.

Results In total, 185 treatment cycles were evaluable. Severe myelosuppression was the main toxicity occurring in 90% of the cycles. Febrile neutropenia or documented infection was found in less than 40%. Two patients died related to treatment (TRM, 1.7%). Nephrotoxicity did not exceed CTC grade 3, which occurred in four cycles only (2.2%). Complete (CR) or partial (PR) responses after mDHAP were documented in 16% and 39% (overall response rate 55%). Harvest of autologous stem cells was successful in 94 (79%) patients and 85 patients (71%) proceeded to stem-cell transplantation. The median overall and progression-free survival was 50.8 and 25.8 months.

Conclusions An improvement in efficacy could not be observed after modified DHAP regimen; however, manageable toxicity and reduced renal complications suggest further investigation. The study, however, also underlines the need for new concepts in the management of advanced and high-risk lymphomas.

Keywords Lymphoma · Salvagetherapy · DHAP · Nephrotoxicity

Introduction

The use of targeted and cellular therapies in patients with refractory or relapsed lymphomas is an expanding field. However, old-school chemotherapy for debulking or bridging is still required in many cases.

The DHAP regimen including dexamethasone, high-dose cytarabine, and cisplatin is well established in the treatment of this population (Velasquez et al. 1988; Philip et al. 1995; Josting et al. 2005, 2010; Abali et al. 2008; Gisselbrecht et al. 2010; Crump et al. 2014). Reported overall response rates after 2–3 cycles range from 45 to 70%, but only about 50% of responding patients can be cured by subsequent stem-cell transplant. Severe myelosuppression and infections are common adverse events after DHAP cycles and may cause treatment-related mortality (TRM) in few cases. Transient or permanent renal dysfunction occurred in up to 20% of treated patients and is mainly attributable to single-day cisplatin infusion.

After we had seen a favourable non-hematological toxicity profile of salvage regimens containing continuous infusions of cisplatin and adriamycin (ASHAP) (Hänel et al. 2000), and cisplatin and cytarabine (MIFAP) (Hänel et al. 2001), we started to use routinely a modified DHAP (mDHAP) protocol with a different dose and administration schedule. Dose splitting (4×25 mg/m^2 instead of 1×100 mg/m^2) and continuous infusion of cisplatin over

✉ Frank Kroschinsky
frank.kroschinsky@uniklinikum-dresden.de

[1] Medical Department I, Dresden University Hospital, Fetscherstr. 74, 01307 Dresden, Germany

[2] Klinikum Chemnitz, Clinic for Internal Medicine III, Bürgerstr. 2, Küchwald, 09113 Chemnitz, Germany

4 days were assumed to have a protective effect, because nephrotoxicity was correlated to peak levels of unbound drug in pharmacokinetic studies (Reece et al. 1987; Nagai et al. 1996; Nagai and Ogata 1997; Erdlenbruch et al. 2001). Prolonged infusion time and fractionated administration of cytarabine (8×0.5 g/m^2 instead of 2×2 g/m^2) might also improve cytotoxicity by increasing the number of exposed lymphoma cells, because both drugs act specifically during S-phase. In addition, it has been postulated that this administration schedule leads to an optimal utilization of the formerly described intracellular synergy between cisplatin and cytarabine (Bergerat et al. 1981; Vadi and Drewinko 1986; Swinnen et al. 1989; Albain et al. 1990). We applied these experiences in the modified DHAP regimen and hypothesized to improve protocol safety as well as treatment outcome.

Patients and methods

Patients

We retrospectively analysed 119 adult patients with relapsed or refractory Hodgkin's or non-Hodgkin's lymphoma who were uniformly treated with the modified DHAP regimen at Dresden University Hospital between 2004 and 2014. The study was approved by the institutional review boards (IRB, EK 186052014). Informed consent was obtained from each individual patient.

Characteristics of the patient population are presented in Table 1. The diagnosis of relapsed or refractory disease was based on physical examination, CT (± PET) scans and lab findings. Disease histology was proven by biopsy at initial diagnosis and repeated in the majority of patients ($n = 70$, 59%) at relapse or disease progression.

Table 1 Patient population: demographics, histological types of lymphoma, disease history, and previous treatments

Total number of pts [*n*]	119
Median age (range) [years]	56 (18–73)
Gender (female/male) [*n*]	78/41
Disease histology [*n* (%)]	
Aggressive B-cell lymphoma	45 (38%)
Indolent B-cell lymphoma	30 (25%)
Mantle-cell lymphoma	10 (8%)
Peripheral T-cell lymphoma	15 (13%)
Hodgkin's lymphoma	19 (16%)
Treatment indication [*n* (%)]	
Early relapse	56 (47%)
Later relapse	40 (34%)
First relapse	77 (65%)
≥ 2nd relapse	19 (16%)
Refractory disease	7 (6%)
Missing	16 (13%)
Ann Arbor stage [*n* (%)]	
I/II	30 (26%)
III/IV	73 (61%)
Missing	16 (13%)
Bone-marrow involvement [*n* (%)]	25 (21%)
Extranodal disease [*n* (%)]	33 (28%)
Previous lymphoma treatment	
Anthracyclines	108 (91%)
Cytarabine	12 (10%)
Platinum derivates	2 (2%)
Rituximab	77 (65%)
Median number of previous chemo cycles (range)	6 (2–23)
Radiotherapy	34 (29%)

ABL aggressive B-cell lymphoma (diffuse-large B-cell lymphoma, primary mediastinal large B-cell lymphoma, plasmablastic lymphoma, ALK + large B-cell lymphoma, Burkitt lymphoma, and follicular lymphoma G3), *IBL* indolent B-cell lymphoma (follicular lymphoma G1/G2, B-PLL, lymphoplasmacytic lymphoma, MALT lymphoma, and nodal marginal zone lymphoma), *MCL* mantle-cell lymphoma, peripheral T-cell lymphoma (enteropathy-associated T-cell lymphoma, PTCL not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma), *HL* Hodgkin's lymphoma

Treatment protocol, staging procedures, and subgroups

The detailed schedule for cytotoxic treatment is described in Table 2. Chemotherapy was given in combination with rituximab (375 mg/m^2 day 0) in patients with CD20 + B-cell lymphomas. G-CSF was started intravenously on day 7 at a dose of 5 µg/kg × day and increased to 10 µg/kg × day after nadir in cycles with stem-cell mobilization. Antimicrobial prophylaxis included levofloxacin, fluconazol, and aciclovir. Hydration, antiemetic drugs, and blood transfusions were given due to common practice. Apheresis of autologous peripheral blood stem cells was performed after the first and/or the second treatment cycles.

Responding patients who were suitable for intensive consolidation strategies received autologous or allogeneic stem transplantation. Preparative regimen for autografting was standard BEAM (Mills et al. 2019) in the majority of patients. Allogeneic patients underwent myeloablative or dose-reduced conditioning and received peripheral blood stem cells from HLA-matched siblings and unrelated donors.

Staging included physical examination, lab values, CT scans, and bone-marrow histology and was performed initially and after completion of therapy. Response of the involved sites was checked after each salvage cycle. Due to the retrospective design, safety analysis focused on the detailed description of hematological toxicity and infections, while non-hematological adverse events were recorded

Table 2 Treatment schedule of modified DHAP (mDHAP) regimen in comparison to standard protocol (DHAP)

	DHAP	mDHAP	Cumulative dose per cycle
Dexamethasone	40 mg p.o./i.v. day 1–4	40 mg i.v. (15 min) day 1–4	160 mg
Cisplatin	100 g/m² c.i. (24 h) day 1	25 mg/m² c.i. (24 h) day 1–4	100 mg/m²
Cytarabin	2×2 g/m² i.v. (3 h) day 2	2×0.5 g/m² i.v. (1 h) day 1–4	4 g/m²

p.o. orally, *i.v.* intra venously, *c.i.* continous infusion

qualitatively. Renal function was evaluated and monitored by serum creatinine level and glomerular filtration rate (GFR), and liver tests included bilirubin and alanine aminotransferase (ALT). Audiometry was not mandatory to be performed before start of chemotherapy.

Treatment response and survival were analysed in cohorts of patients with different but biologically similar types of lymphomas. Table 1 shows in detail the histological entities which were summarized as aggressive or indolent B-cell lymphomas (ABL, IBL) and peripheral T-cell lymphomas (PTCL), respectively. Patients with mantle-cell lymphomas (MCL) and Hodgkin's lymphomas (HL) were regarded separately.

Statistics

Patient and treatment data were extracted from hard copy or electronic files and collected to an REDCap® database web application (Harris et al. 2009). Descriptive and exploratory analyses were done with statistics program R® (Chida et al. 2014). Results are presented as medians with ranges and analysed using χ^2 test or Mann–Whitney U test. A p value of less than 0.05 was considered significant. Survival was tabulated using the method of Kaplan and Meier (1958). The effect of different factors on survival was tested by univariate analysis using the log-rank test (Peto and Peto 1972). Overall survival was calculated from the first day of first mDHAP cycle until death or last contact. Relapse and death from any cause were regarded as events. Cox-hazard logistic regression analyses were conducted to determine independent predictors of mortality and long-term survival.

Results

Toxicity

The patients received in median two cycles of mDHAP (range 1–3) resulting in total numbers of 185 treatment cycles. Rituximab was given in 79 out of 85 patients with B-cell lymphomas (90% of cycles). Median interval between cycles was 34 (range 25–98) days. Two patients died from treatment-related complications indicating a mortality rates (TRM) of 1.7%. Chemotherapy had to be discontinued in 5 (4.2%) cases due to adverse events. Table 3 summarizes the hematological toxicity and related complications. Pegylated or non-pegylated G-CSF was given in 178 (96%) cycles. Two units in median of red cells (range 0–23) and platelets (range 0–22) had to be transfused per cycle. The median duration of severe neutropenia (ANC $< 1.0 \times 10^9$/L) was 6 days (range 0–47). The median number of days with temperature > 38.0 °C in febrile patients was two (range 1–30).

A clinically significant impairment of renal function occurred in nine cycles, only four cases (2.2%) were classified as CTC grade 3 (based on worsening of creatinine and/or glomerular filtration rate). Renal function recovered in most cases with conservative management only. One patient

Table 3 Toxicities (according to CTC criteria) and related morbidity

Parameter	Number (%) of cycles
Leukocytopenia	
No/not severe	13 (7.0)
Grade 3	12 (6.5)
Grade 4	160 (86.5)
Neutropenia	
No/not severe	18 (10.0)
Grade 3	5 (3.0)
Grade 4	161 (87.0)
Thrombocytopenia	
No/not severe	18 (9.7)
Grade 3	4 (2.2)
Grade 4	163 (88.1)
Fever and infections	
Fever of unknown origin (FUO)	40 (21.6)
Fever with documented infection	26 (14.1)
SIRS/sepsis	19 (10.3)
Creatinin	
No/not severe	183 (98.9)
Grade 3	2 (1.1)
Grade 4	0
GFR	
No/not severe	181 (97.8)
Grade 3	4 (2.2)
Grade 4	0

required hemofiltration during Gram-negative sepsis and multiorgan dysfunction.

Treatment response

Out of 119 patients, 110 were evaluable for response evaluation. A complete or partial response (CR, PR) after salvage therapy was achieved in 18 (16%) and 47 (39%) patients, resulting in an overall response rate of 55%. No change or progressive disease had to be documented in 29 (24%) and 16 (13%) patients, respectively. Mobilization and harvest of autologous stem cells were successful in 94 (79%) patients. Poor mobilization was observed in three cases. Other patients did not undergo stem-cell collection due to toxicity or disease progression ($n=11$) if they were primary scheduled for allogeneic transplantation ($n=8$) or if harvest had already been performed previously in treatment course ($n=3$). Eighty-five patients underwent autologous ($n=48$, 40%), allogeneic ($n=12$, 10%), or auto-allo ($n=25$, 21%) transplantation ($n=37$, $n=8$, and $n=14$ patients were mDHAP responders). Response rates depending on lymphoma type and in different transplant settings are presented in Table 4.

Survival

After a median follow-up of 64 months, 54 patients (45%) are alive, 61 patients (51%) died, and four patients (3%) are lost for follow-up. Reason for death was lymphoma in 48 cases (79%). Thirty-five (65%) of living patients were in continuing remission at the last follow-up. This results in medians of overall (OS) and progression-free survival (PFS) of 50.8 and 25.8 months.

Survival was different between the types of lymphoma, which is shown in Fig. 1. Best outcome was observed in the Hodgkin's lymphoma cohort (median OS 70.7 months, median PFS 61.4 months), while treatment results were dismal in patients with PTCL (median OS 15.5 months, median PFS 10.8 months). Patients with aggressive B-cell-lymphomas, which was the largest subgroup in our study, had medians of OS and PFS of 28.5 and 20.2 months, respectively.

Discussion

The primary aim of this retrospective study was to evaluate feasibility and safety of a dose and administration schedule-modified DHAP regimen.

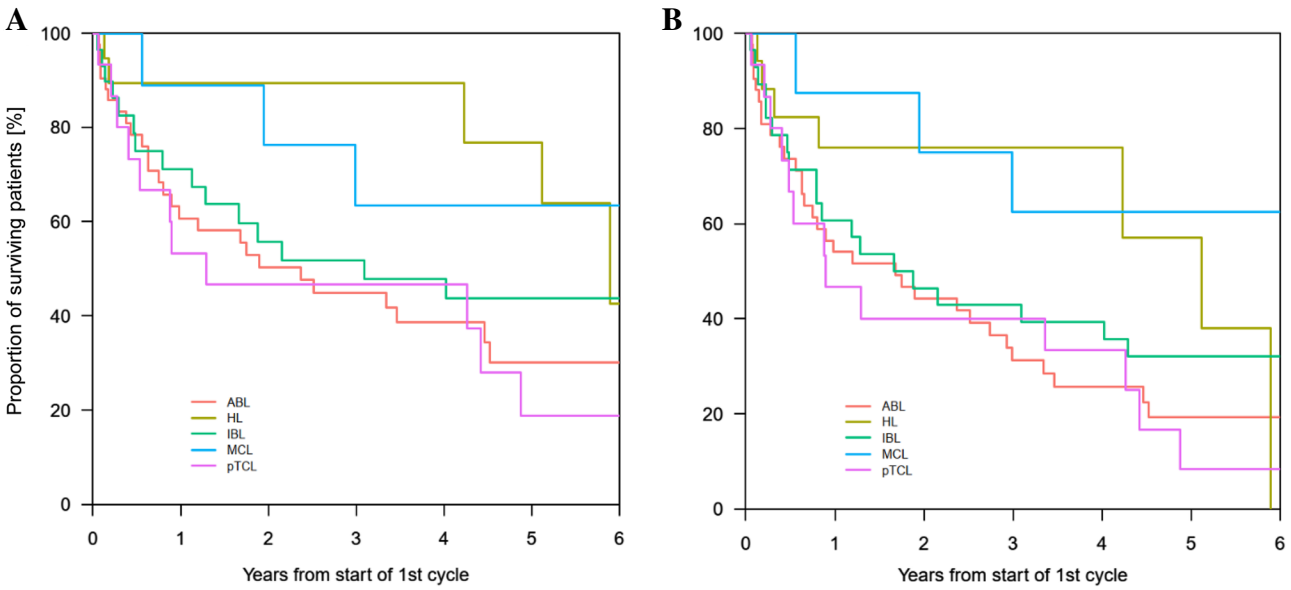
Only two out of 119 patients (1.7%) died related to treatment after the modified regimen compared to ten out of 90 cases (11%) in the series with standard DHAP initially published by Velasquez et al. (1988). Modified DHAP induced substantial myelosuppression with grade 3 or 4 thrombocytopenia and granulocytopenia occurring in about 90% of the cycles which seems to be slightly more pronounced compared to other reports. However, patients developed fever

Table 4 Response rates after modified DHAP therapy depending on lymphoma type and consecutive transplant procedure

Depending on	Complete response *n* (%)	Partial response *n* (%)	Stable disease *n* (%)	Progressive disease *n* (%)
Type of lymphoma				
ABL ($n=45$)	8 (17)	19 (42)	8 (17)	7 (15)
IBL ($n=30$)	3 (10)	11 (37)	10 (33)	2 (7)
MCL ($n=10$)	1 (10)	4 (40)	4 (40)	1 (10)
PTCL ($n=15$)	2 (14)	4 (27)	5 (33)	3 (20)
HL ($n=19$)	4 (21)	9 (47)	2 (11)	3 (16)
Type of transplant				
Autologous ($n=48$)	10 (22)	27 (56)	7 (15)	1 (2)
Allogeneic ($n=12$)	3 (25)	5 (42)	3 (25)	0 (0)
Auto-allo ($n=25$)	3 (12)	11 (44)	7 (28)	4 (16)
Any transplant ($n=85$)	16 (19)	43 (50)	17 (20)	5 (6)
No transplant ($n=34$)	2 (6)	4 (12)	12 (35)	11 (32)

Responses were evaluable in 110 patients (information is missing in nine patients, among them two cases of TRM)

ABL aggressive B-cell lymphoma (diffuse-large B-cell lymphoma, primary mediastinal large B-cell lymphoma, plasmablastic lymphoma, ALK + large B-cell lymphoma, Burkitt lymphoma, and follicular lymphoma G3), *IBL* indolent B-cell lymphoma (follicular lymphoma G1/G2, B-PLL, lymphoplasmacytic lymphoma, MALT lymphoma, and nodal marginal zone lymphoma), *MCL* mantle-cell lymphoma; PTCL—peripheral T-cell lymphoma (enteropathy-associated T-cell lymphoma, PTCL not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma), *HL* Hodgkin's lymphoma



ABL – aggressive B-cell lymphoma (diffuse-large B-cell lymphoma, primary mediastinal large B-cell lymphoma, plasmablastic lymphoma, ALK+ large B-cell lymphoma, Burkitt lympoma, follicular lymphoma G3); IBL – indolent B-cell lymphoma (follicular lymphoma G1/G2, B-PLL, lymphoplasmacytic lymphoma, MALT lymphoma, nodal marginal zone lymphoma); MCL – mantle-cell lymphoma; PTCL – peripheral T-cell lymphoma (enteropathy-associated T-cell lymphoma, PTCL not otherwise specified, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma); HL – Hodgkin's lymphoma.

Fig. 1 Overall (**a**) and progression-free (**b**) survival in different lymphoma types

in less than 40% and only about 10% fulfilled the criteria of SIRS or sepsis.

Nephrotoxicity in our series did not exceed CTC grade 3, which occurred in four cycles only (2.2%). None of the patients developed a persistent impairment of renal function of clinically relevance. Among the patients treated with standard DHAP and rituximab in the CORAL trial, which is the most recent study in this field, 11 patients (6%) experienced nephrotoxicity grade 3 or 4 (Gisselbrecht et al. 2010). A phase-2-trial which evaluated R-DHAP for relapsed or refractory lymphomas in 57 patients reported grade 3/4 renal dysfunctions in 11% (Witzig et al. 2008). Even in patients treated with the ESHAP regimen which also investigated a 96-h infusion of cisplatin, a reversible and permanent increase of creatinine level was observed in 18% and 4% of the patients (Velasquez et al. 1994). Thus, it has to be assumed that renal toxicity of cisplatin-based regimens is also influenced by the other cytotoxic drugs combined in the protocols (cytarabine and etoposide in DHAP and ESHAP, respectively).

However, these are historical comparisons of heterogeneous cohorts of lymphoma patients, treated at different centres, according to different policies and the interval between the studies is more than 10 years. The higher proportion of heavily pretreated patients with indolent lymphomas could have contributed to the extensive hematologic toxicity in our series. Furthermore, about half of the patients received DHAP in combination with rituximab, and immuno chemotherapy has shown to cause slightly deeper myelosuppression than chemotherapy alone in some of the large comparative trials (Coiffier et al. 2002; Hiddemann et al. 2005).

The overall response rate of 55% in this series and the observation, that the majority of responses were incomplete (CR 16%, PR 39%) are comparable to other papers. The corresponding results for OR, CR and PR with the standard regimen as reported from Velasquez were 55%, 31% and 24% (Velasquez et al. 1988). Response rates in other studies with different types of lymphomas range from 44% (CR 14%, PR 30%) (Crump et al. 2014) to 82% (CR 33%, PR 49%) (Witzig et al. 2008), and were found at 63% (CR 28%, PR 35%) in the CORAL population with only DLBCL patients after R-DHAP (Gisselbrecht et al. 2010). The majority of patients in this study could proceed to stem-cell transplantation. This emphasizes the safety of the protocol and is important, as only the transplant opens the chance for cure in this population.

The interpretation of our results should also take into consideration the very poor prognosis of the cohort with a high number of early relapses, refractory diseases, and heavily pretreated patients. Recent trials demonstrated an

improved outcome of patients with mantle-cell lymphomas, who had received cytarabine as part of the first line treatment (Romaguera et al. 2010; Geisler 2010; Hermine et al. 2016). For these patients, the role of a cytarabine-containing salvage regimen is questionable.

The inhomogeneous patient population in terms of disease histology and risk factors, as well as the retrospective evaluation of a cohort, whose treatment is up to 10 years ago, are major limitations of this study. We did not perform systematic central reviews of pathology or response evaluation. The number of patients is too low to draw definite conclusions for several subgroups. Although the postulated improvement in efficacy could not be observed, we could demonstrate that our modification of DHAP regimen is less toxic on renal function and hematological toxicity was manageable. Therefore, further investigation is justified and recommended.

The study, however, also underlines the need for new concepts in the management of advanced and high-risk lymphomas including, beside chemotherapy, targeted, and cellular approaches.

Compliance with ethical standards

Conflict of interest None.

References

Abali H, Ürün Y, Öksüzoğlu B et al (2008) Comparison of ICE (Ifosfamide–Carboplatin–Etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Invest 26:401–406. https://doi.org/10.1080/07357900701788098

Albain KS, Swinnen LJ, Erickson LC et al (1990) Cisplatin preceded by concurrent cytarabine and hydroxyurea: a pilot study based on an in vitro model. Cancer Chemother Pharmacol 27:33–40. https://doi.org/10.1007/BF00689273

Bergerat J, Drewinko B, Corry P et al (1981) Synergistic lethal effect of *cis*-dichlorodiammineplatinum and 1-β-D-arabinofuranosylcytosine. Cancer Res 41:25–30

Chida K, Morohashi G, Fuji H et al (2014) Implementation and evaluation of an efficient secure computation system using "R" for healthcare statistics. J Am Med Informatics Assoc 21:326–331. https://doi.org/10.1136/amiajnl-2014-002631

Coiffier B, Lepage E, Brière J 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

Crump M, Kuruvilla J, Couban S et al (2014) Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol 32:3490–3496. https://doi.org/10.1200/JCO.2013.53.9593

Erdlenbruch B, Nier M, Kern W et al (2001) Pharmacokinetics of cisplatin and relation to nephrotoxicity in paediatric patients. Eur J Clin Pharmacol 57:393–402. https://doi.org/10.1007/s002280100319

Geisler CH (2010) Front-line treatment of mantle cell lymphoma. Haematologica 95:1241–1243. https://doi.org/10.3324/haematol.2010.025627

Gisselbrecht C, Glass B, Mounier N et al (2010) Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 28:4184–4190. https://doi.org/10.1200/JCO.2010.28.1618

Hänel M, Kröger N, Hoffknecht MM et al (2000) ASHAP is an effective salvage therapy for recurrent and refractory malignant lymphomas. Ann Hematol 79:304–311

Hänel M, Kröger N, Kroschinsky F et al (2001) Salvage chemotherapy with mitoxantrone, fludarabine, cytarabine, and cisplatin (MIFAP) in relapsing and refractory lymphoma. J Cancer Res Clin Oncol 127:387–395. https://doi.org/10.1007/s004320000226

Harris PA, Taylor R, Thielke R et al (2009) Research electronic data capture (REDCap)—a metadata driven methodology and workflow process for providing translational research informatict support. J Biomed Inform 42:377–381. https://doi.org/10.1016/j.jbi.2008.08.010.Research

Hermine O, Hoster E, Walewski J et al (2016) Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma N. Lancet 388:565–575. https://doi.org/10.1016/S0140-6736(16)00739-X

Hiddemann W, Kneba M, Dreyling M et al (2005) Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: re. Blood 106:3725–3732

Josting A, Sieniawski M, Glossmann JP et al (2005) High-dose sequential chemotherapy followed by autologous stem cell transplantation in relapsed and refractory aggressive non-Hodgkin's lymphoma: results of a multicenter phase II study. Ann Oncol 16:1359–1365. https://doi.org/10.1093/annonc/mdi248

Josting A, Müller H, Borchmann P et al (2010) Dose intensity of chemotherapy in patients with relapsed Hodgkin's lymphoma. J Clin Oncol 28:5074–5080. https://doi.org/10.1200/JCO.2010.30.5771

Kaplan E, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Ass 53(282):457–481

Mills BW, Chopra R, Mcmillan A et al (2019) BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol 13:588–595

Nagai N, Ogata H (1997) Quantitative relationship between pharmacokinetics of unchange cisplatin and nephrotoxicity in rats: importance of area under the concentration-time curve (AUC) as the major toxicodynamic determinant in vivo. Cancer Chemother Pharmacol 40:11–18. https://doi.org/10.1007/s002800050618

Nagai N, Kinoshita M, Ogata H et al (1996) Relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity after intravenous infusions of cisplatin to cancer patients. Cancer Chemother Pharmacol 39:131–137. https://doi.org/10.1007/s002800050548

Peto R, Peto J (1972) Asymptotically efficient rank invariant test procedures (with discussion). J R Stat Soc 135:185–207

Philip T, Guglielmi C, Hagenbeek A et al (1995) Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin'S lymphoma. N Engl J Med 333:1540–1545

Reece PA, Stafford I, Russell J et al (1987) Creatinine clearance as a predictor of ultrafilterable platinum disposition in cancer patients treated with cisplatin: relationship between peak ultrafilterable platinum plasma levels and nephrotoxicity. J Clin Oncol 5:304–309. https://doi.org/10.1200/JCO.1987.5.2.304

Romaguera JE, Fayad LE, Feng L et al (2010) Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol 150:200–208. https://doi.org/10.1111/j.1365-2141.2010.08228.x

Swinnen LJ, Barnes DM, Fisher SG et al (1989) 1-b-D-arabinofuranosylcytosine and hydroxyurea production of cytotoxic synergy with cis-diamminedichloroplatinum (II) and modification of palitnum-DNA interstrand crosslinking. Cancer Res 49:1383–1389

Vadi H, Drewinko B (1986) Kinetics and mechanism of the 1-beta-D-arabinofuranosylcytosine-induced potentiation of *cis*-diamminedichloroplatinum (II) cytotoxicity. Cancer Res 46:1105–1109

Velasquez WS, Cabanillas F, Salvador P et al (1988) Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 71:117–122

Velasquez W, McLaughlin P, Tucker S et al (1994) ESHAP—an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 12:1169–1176

Witzig TE, Geyer SM, Kurtin PJ et al (2008) Salvage chemotherapy with rituximab DHAP for relapsed non-Hodgkin lymphoma: a phase II trial in the north central cancer treatment group. Leuk Lymphoma 49:1074–1080. https://doi.org/10.1080/10428190801993470