Received: 3 March 2021 | Revised: 17 April 2021 | Accepted: 22 April 2021

DOI: 10.1111/cas.14933

REVIEW ARTICLE

Cancer Science WILEY

Chemotherapy for non-Hodgkin lymphoma in the hemodialysis patient: A comprehensive review

Hajime Yasuda[1] | Mutsuko Yasuda[2] | Norio Komatsu[1]

[1]Department of Hematology, Juntendo University School of Medicine, Tokyo, Japan

[2]Department of Endocrinology and Metabolism, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan

Correspondence
Hajime Yasuda, Department of Hematology, Juntendo University School of Medicine, Address: 2-1-1 Hongou, Bunkyo-ku, Tokyo, 113-8421 Japan.
Email: hyasuda@juntendo.ac.jp

Abstract

Chemotherapy for non-Hodgkin lymphoma (NHL) in the hemodialysis (HD) patient is a challenging situation. Because many drugs are predominantly eliminated by the kidneys, chemotherapy in the HD patient requires special considerations concerning dose adjustments to avoid overdose and toxicities. Conversely, some drugs are removed by HD and may expose the patient to undertreatment, therefore the timing of drug administration in relation to HD sessions must be carefully planned. Also, the metabolites of some drugs show different toxicities and dialysability as compared with the parent drug, therefore this must also be catered for. However, the pharmacokinetics of many chemotherapeutics and their metabolites in HD patients are unknown, and the fact that NHL patients are often treated with distinct multiagent chemotherapy regimens makes the situation more complicated. In a realm where uncertainty prevails, case reports and case series reporting on actual treatment and outcomes are extremely valuable and can aid physicians in decision making from drug selection to dosing. We carried out an exhaustive review of the literature and adopted 48 manuscripts consisting of 66 HD patients undergoing 71 chemotherapy regimens for NHL, summarized the data, and provide recommendations concerning dose adjustments and timing of administration for individual chemotherapeutics where possible. The chemotherapy regimens studied in this review include, but are not limited to, rituximab, cyclophosphamide + vincristine + prednisolone (CVP) and cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP)-like regimens, chlorambucil, ibrutinib, bendamustine, methotrexate, platinum compounds, cytarabine, gemcitabine, etoposide, ifosfamide, melphalan, busulfan, fludarabine, mogamulizumab, brentuximab vedotin, and ^{90}Y-ibritumomab tiuxetan.

KEYWORDS

DLBCL, end-stage renal disease, ESRD, R-CHOP, renal replacement therapy

Abbreviations: Ara-C, cytarabine; AUC, area under the concentration-time curve; BR, bendamustine + rituximab; BTK, Bruton tyrosine kinase; BU, busulfan; BV, brentuximab vedotin; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisolone; CNS, central nervous system; CPA, cyclophosphamide; CR, complete response; CVP, cyclophosphamide + vincristine + prednisolone; DXR, doxorubicin; ESRD, end-stage renal disease; FLU, fludarabine; GDC, gemcitabine + dexamethasone + carboplatin); GemOx, gemcitabine + oxaliplatin; GFR, glomerular filtration rate; HD, hemodialysis; HSCT, hematopoietic stem cell transplantation; IDEC-Y2B8, 90Y-ibritumomab tiuxetan; MEL, melphalan; MMAE, microtubule-disrupting agent monomethyl auristatin E; MMF, mycophenolate mofetil; MTX, methotrexate; NHL, non-Hodgkin lymphoma; proMACE/CytaBOM, prednisolone + methotrexate + doxorubicin + cyclophosphamide + etoposide/cytarabine + bleomycin + vincristine + methotrexate; PSL, prednisolone; TLS, tumor lysis syndrome; VCR, vincristine.

1 | INTRODUCTION

In an era where the number of hemodialysis (HD) patients is on the rise and the life expectancy of such patients is prolonged, the incidence of encountering non-Hodgkin lymphoma (NHL) patients on HD increases. Furthermore, patients on HD have been reported to have an increased risk of developing NHL compared to the general population.[1] Also, renal invasion of lymphoma has been reported in 6%-60% of autopsy cases of which approximately 0.5% showed renal failure, and therefore the lymphoma itself may be the cause renal failure requiring HD.[2] However, because HD patients are often excluded from clinical trials, information on the safety and efficacy of chemotherapy for HD patients with NHL is limited. The pharmacokinetics of many chemotherapeutics in HD patients are unknown, and the fact that NHL patients are often treated with distinct multiagent chemotherapy makes the situation even more complicated. Under such circumstances, reports of actual drug administrations and outcomes are heavily relied on for a source of information, and the bulk of evidence comes from case reports and case series, which are sparsely scattered among the literature. We carried out an exhaustive review of the literature and collected existing evidence to aid physicians confronted with this challenging situation.

2 | MATERIALS AND METHODS

We conducted a MEDLINE database search through PubMed using a combination of key words "lymphoma" and "dialysis". Titles and abstracts were first studied, and only English reports of patients undergoing treatment for NHL and concomitant HD were considered. Subsequently, full reading of all considered manuscripts was carried out, ultimately leading to the adoption of 48 manuscripts including 66 patients treated with 71 regimens. No limits were made concerning the published year of the manuscript, and the most recent PubMed search was conducted in February 2021. Information from adopted manuscripts was extracted concerning last name of first reporter, reported year, patient sex, patient age, type of NHL, treatment regimen, chemotherapy dosing, number of treatment courses under HD, type of adverse events, treatment response, and outcome (survival). Adverse events were assessed as "not available (N/A)" in manuscripts not specifically stating the absence of adverse events. Where possible, grading of adverse events was done in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

3 | GENERAL CONSIDERATIONS

Most chemotherapeutics are not recommended for use in HD patients to begin with, and as a prerequisite chemotherapy should be avoided whenever possible in HD patients. Patients on HD are frailer than the general population, and are often accommodated by comorbidities such as hypertension, heart disease, diabetes mellitus, and anemia. Furthermore, HD patients are prone to infections, and therefore are extremely disadvantaged in the setting of chemotherapy-requiring NHL.[3]

Besides patient-specific characteristics, chemotherapy for the HD patient requires special considerations concerning dose adjustments and timing of drug administration in relation to HD sessions. Many drugs are predominantly eliminated by the kidneys, and in such drugs standard dosing may cause overdose and toxicities in HD patients. On the other hand, HD may remove excessive amounts of drug, exposing the patient to undertreatment. Therefore, drug dialysability must also be taken into account and chemotherapy should basically be administered after or on a day without HD for drugs that are eliminated by HD. In some instances, partial drug removal through HD may be purposefully carried out to improve drug tolerance or to remove remnants of drug that have not distributed to the targeted tissue and could present as a potential cause of toxicities.[4,5] Also, in patients with high risk of TLS, the routine number of HD sessions may not be sufficient following chemotherapy, and short-term daily HD sessions may be required to avoid life-threatening conditions such as hyperkalemia.[6]

Many factors influence drug dialysability. Important drug-related factors include molecular weight (drugs with smaller molecular weight are more easily dialyzed), protein binding (drugs with low protein binding are more easily dialyzed), volume of distribution (drugs with high volume of distribution are less dialyzed because of constant drug return from extravascular tissues), and affinity to red blood cells (red blood cells may act as nondialyzable drug carriers). Important HD-related factors include duration of HD sessions (more drug is dialyzed with longer sessions), and surface area and membrane thickness of the dialyzer.[7] The new high-flux membranes that are now routinely used can remove drugs with higher molecular weight, and as a result of such advances in HD technology it is vital to keep in mind that some older reports concerning dose reductions in HD patients before the year 2000 are likely to be outdated and inaccurate for current day practice.[4,7,8]

Another important factor to keep in mind are the distinct traits of the drug metabolites, which may not show the same toxic profiles and dialysability as the parent drug. Conversely, if the parent drug is rapidly degraded to nontoxic metabolites, ESRD requiring HD may not be an obstacle in administration of such drugs.[9]

Considering the complexity of factors that are involved in dialysability of drugs and their metabolites, actual pharmacokinetic studies in HD patients are of extreme value but are lacking for many drugs, and chemotherapeutics are one of the least studied classes of drugs. In a realm where uncertainty rules, reports of actual administrations, adverse events, and outcomes of individual treatment methods can help guide physicians in decision making from drug selection to dosing for NHL patients on HD.

4 | INDIVIDUAL TREATMENT METHODS

Case reports and case series reporting on actual treatment of NHL patients on HD are shown in Table 1 (rituximab, CVP, and CHOP),[2,3,6,10-35] Table 2 (various other regimens),[10,19,25,34-51] and Table 3 (stem cell transplantation),[34,52-54] and are discussed below. Recommendations on individual drug administrations are summarized in Table 4.[3-5,9-11,19,25,38,39,43-46,55-60] Despite the possible bias of case reports favoring cases with good outcomes, overall the rates of adverse events are high and outcomes of the extracted cases are dismal compared to their counterparts not on HD. Therefore, our recommendations do not apply to all HD patients with NHL and treatment indications should be carefully considered in individual patients. Furthermore, although reports on HD patients receiving CVP and CHOP-like regimens with or without rituximab are abundant, there are few reports on other chemotherapeutics, which is a limitation that readers must keep in mind.

4.1 | Rituximab, CVP, and CHOP

Rituximab is a chimeric anti-CD20 monoclonal antibody used for a wide range of B-cell NHLs. Rituximab is administered both as monotherapy and also in conjunction with various regimens including CVP and CHOP-like regimens. Rituximab monotherapy was administered to two NHL patients on HD in the literature (cases 1 and 2). Serum rituximab levels in these HD patients were comparable to those of patients with normal renal function, and rituximab was found to be absent in the dialysate fluid.[10,11] Therefore, rituximab may be administered before or after HD sessions and dose adjustments are not necessary.

CVP and CHOP-like regimens are used as standard first-line treatment in a wide range of NHLs. A standard CVP regimen consists of day 1 VCR 1.4 mg/m^2, day 1 CPA 750 mg/m^2, and days 1-5 PSL 40 mg/m^2 (100 mg/body in some cases). A standard CHOP regimen consists of day 1 VCR 1.4 mg/m^2, day 1 DXR 50 mg/m^2, day 1 CPA 750 mg/m^2, and days 1-5 PSL 100 mg/body. VCR is a vinca alkaloid primarily metabolized in the liver. VCR and its metabolites are reported to be secreted 69% in feces and 12% in urine at 72 h after administration.[61] The anthracycline DXR and its major metabolite doxorubicinol are not predominantly eliminated by the kidneys, but the AUCs of DXR and doxorubicinol have been found to be higher in HD patients compared to non-HD patients.[62] Some investigators have recommended a 10%-20% dose reduction of DXR and VCR in HD patients,[27] while most others have recommended the standard dose.[3,25] Data concerning removal of DXR and VCR by HD are limited, and therefore these drugs should be administered after HD.[3,4] CPA is an alkylating agent that undergoes biotransformation to an active metabolite in the liver. The plasma half-life of CPA varies considerably between individuals, and ranges from 1.8 to 9.2 h.[63] Approximately 30%-60% of CPA is eliminated by the kidneys as the parent drug or its metabolites,[64] and a dose reduction of 25% has been recommended in HD patients.[4] CPA is removed by dialysis and therefore should be administered after HD sessions.[4,5] Milsted et al reported that little CPA was lost in the dialysate, and therefore the investigators suggested that HD need not be interrupted during CPA administration, but this is an old report from 1978 and their results may reflect the premature technical capabilities of HD from the time of reporting (see also section 3).[13]

There are many reports of NHL patients treated with CVP and CHOP-like regimens with or without rituximab in the literature. Besides case reports, there are two case series that show conflicting results as to the toxicity and tolerability of CHOP-like regimens with or without rituximab in HD patients. Ochi et al reported that although out of six patients (cases 28-32 and 43), three experienced grade 3 anemia and four experienced grade 3 infections including febrile neutropenia, all patients completed their scheduled three to eight courses of chemotherapy and it was concluded that R-CHOP-like therapy was well tolerated and effective in HD patients.[3] Conversely, Hamadah et al reported eight NHL patients on HD (cases 19-22 and 33-36) treated with CHOP-like regimens with or without rituximab, and only two patients were able to complete their full six courses of therapy. In this study, five patients were able to complete only one course, and one patient was able to complete only three courses of CHOP-like therapy with or without rituximab due to chemotherapy-related toxicities.[25] This discrepancy between the two studies may be due to the fact that Ochi et al carried out significant dose reductions of DXR, pirarubicin, VCR, and CPA in patients aged 70 years and over, 30% dose reductions for patients aged 70-79 years, and 50% dose reductions for patients aged 80 years and over.[3] Compared to this, although the median age was high at 70 years (range 46-83) in the study by Hamadah et al, they only carried out 0%-50% dose reductions of CPA, and the other agents of CHOP were given at full dose.[25] Dose reductions according to age are often carried out even in patients with normal renal function, and we interpret from the results of the two case series reported by Ochi and Hamadah et al that dose reductions for CHOP should be carried out according to age rather than whether the patient is on HD or not.

In the literature, CVP and CHOP-like therapy with or without rituximab was administered to a total of 37 patients (cases 7-43), of which 14 patients experienced infections, four patients experienced TLS or hyperkalemia, and eight patients were dead at time of reporting despite the overall short follow-up period. Information on adverse events and survival were missing in 12 and three patients, respectively, and therefore the actual numbers are probably even worse. From these results, it can be interpreted that CVP and CHOP-like therapy with or without rituximab is a harsh treatment method for HD patients. Where there is a choice of treatment as is the case in indolent NHLs, other drugs such as chlorambucil and ibrutinib may be a safer option, but more data are required to draw conclusions.

TABLE 1 Rituximab, CVP, and CHOP-like regimens in hemodialysis patients

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome / time to follow up
1	Jillella et al, 2002[10]	M	54	B-cell NHL	R	375 mg/m^2	8	Hyperkalemia (grade 4)	CR	Alive
2	Morita et al, 2010[11]	M	76	B-cell NHL	R	375 mg/m^2	6	N/A	CR	Died of PD 14 months after diagnosis
3	Ablin et al, 1972[12]	M	12	BL	CPA	3-4 mg/kg/day	12 days	Staphylococcus aureus shunt infection, Klebsiella pneumoniae sepsis (grade 5)	tumor reduction	Died of sepsis on day 58 of hospitalization
4	Milsted et al, 1978[13]	M	27	NHL	CPA	600 mg/body	1	N/A	N/A	N/A
5	Gianviti et al, 1989[14]	M	9	BL	VCR + CPA	N/A	N/A	Abdominal hemorrhage	tumor reduction	Died of abdominal hemorrhage
6	Ozaltin et al, 2004[15]	M	17	B-cell NHL	VCR + CPA + PSL	VCR: 1 mg/m^2 day 1 CPA: 200 mg/m^2 days 1-5 PSL: 60 mg/m^2 days 1-7	1	N/A	PR	Alive
7	Christopoulos et al, 2009[16]	F	65	T-LGLL	CVP	standard	1	Severe sepsis, pulmonary infection	no response	Died of sepsis 6 months later
8	Cavoli et al, 2012[17]	M	72	MZL	CVP	N/A	N/A	N/A	N/A	N/A
9	Miyata et al, 2017[18]	M	77	MCL	CVP	CPA: 325 mg/m^2 VCR: 1.4 mg/m^2 PSL: 100 mg/body days 1-5	6	N/A	N/A	died of pulmonary hemorrhage 8 months from presentation
10	Lin et al, 2009[6]	F	47	DLBCL	VCR + CPA + DEX	VCR 1.8 mg/body CPA 1000 mg/body DEX 40 mg/body [a]	N/A	TLS Hyperkalemia (grade 3)	N/A	N/A
11	Yasuda et al, 2021[19]	M	73	MCL	CVP	CPA: 375 mg/m^2 VCR: 1.4 mg/m^2 PSL: 100 mg/body days 1-5	1	Thrombocytopenia (grade 3)	tumor reduction	proceeded to ibrutinib therapy
12	Weng et al, 2010[20]	F	75	DLBCL	R-CVP	R: 100 mg/body VCR: 2 mg/body CPA: 1000 mg/body PSL: 60 mg/body/day (number of days N/A)	1	N/A	improvement	died of FN during salvage chemotherapy

(Continues)

TABLE 1 (Continued)

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome / time to follow up
13	Ochi et al, 2016[3]	M	69	DLBCL	R-CVP	RDI 83%	6	Neutropenia (grade 4), anemia (grade 3) thrombocytopenia (grade 3), FN (grade 3) PN (grade 3)	CR	alive at 15 months from diagnosis
14	Ochi et al, 2016[3]	M	82	FL	R-CVP	RDI 54%	6	Neutropenia (grade 3)	CR	alive at 34 months from diagnosis
15	Gangireddy et al, 2019[21]	M	80	DLBCL	R-miniCHOP	N/A	N/A	Severe pancytopenia, MOF	N/A	died
16	Paganelli et al, 1989[22]	F	53	NHL	CHOP	N/A	1	Aspergillus pneumonia, shock	N/A	died 3 days after completing 1 course of CHOP
17	Agha-Razii et al, 2000[23]	M	73	BL	CHOP	N/A	1	Pulmonary infection, sepsis	N/A	died on day 3 of CHOP
18	Peddi et al, 2015[24]	M	54	MCL	CHOP	N/A	N/A	N/A	N/A	N/A
19	Hamadah et al, 2017[25]	N/A	N/A	T-cell NHL	CHOP	20% reduction of CPA	1	TLS, infection, AMS	PR	1-month follow up
20	Hamadah et al, 2017[25]	N/A	N/A	DLBCL	CHOP	20% reduction of CPA	1	FN, infection	PR	79-month follow up
21	Hamadah et al, 2017[25]	N/A	N/A	T-cell NHL	CHOP-E	Standard	1	FN, infection, cardiac complication	PD	1-month follow up
22	Hamadah et al, 2017[25]	N/A	N/A	T-cell NHL	CHOP-E	25% reduction of CPA	6	TLS, FN	N/A	5-month follow up
23	de Barros Pontes et al, 2013[26]	M	77	DLBCL	R-miniCHOP + radiotherapy	10% reduction of DXR and CPA	6	Mild congestive heart failure	CR	alive in CR at 11 months
24	Feldmann et al, 2007[27]	M	70	DLBCL	R-CHOP	courses 1 and 2: 50% reduction of DXR and CPA, PSL reduced to 80 mg/ body/day; courses 3-6: standard	6	Severe hyperglycemia	PR	PR after 6 courses of R-CHOP
25	Alkhunaizi et al, 2008[2]	M	47	DLBCL	R-CHOP + radiotherapy	N/A	1	N/A	improvement	alive in CR at 20 months after diagnosis
26	Jorge et al, 2010[28]	F	51	DLBCL	R-CHOP	standard	N/A	N/A	N/A	alive

(Continues)

TABLE 1 (Continued)

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome / time to follow up
27	Kawano et al, 2011[29]	M	64	DLBCL	R-CHOP	50% reduction of DXR and CPA; PSL administered at 60 mg/m^2 days 1-5	R: 4 weekly courses + 4 monthly courses CHOP: 1 course	Psoas hematoma	CR	alive in CR at 27 months
28	Ochi et al, 2016[3]	M	60	DLBCL	R-CHOP	RDI 94%	6	Neutropenia (grade 3), anemia (grade 3), infection (grade 3), PN (grade 3)	CR	alive at 24 months from diagnosis
29	Ochi et al, 2016[3]	M	72	DLBCL	R-CHOP	RDI 63%	6	Neutropenia (grade 4), anemia (grade 3), thrombocytopenia (grade 3), FN (grade 3)	CR	alive at 13 months from diagnosis
30	Ochi et al, 2016[3]	M	80	DLBCL	R-CHOP	RDI 40%	8	Neutropenia (grade 3)	CR	died of PD at 45 months from diagnosis
31	Ochi et al, 2016[3]	M	62	DLBCL	R-CHOP	RDI 87%	8	Neutropenia (grade 3), infection (grade 3)	CR	alive at 15 months from diagnosis
32	Ochi et al, 2016[3]	M	75	DLBCL	R-CHOP +radiotherapy	RDI 57%	3	Neutropenia (grade 4), thrombocytopenia (grade 3)	CR	died in CR of hepatocellular carcinoma 18 months from diagnosis
33	Hamadah et al, 2017[25]	N/A	N/A	DLBCL	R-CHOP	25% reduction of CPA	1	FN, infection	CR	55-month follow up
34	Hamadah et al, 2017[25]	N/A	N/A	High-grade B-cell lymphoma	R-CHOP	Standard	1	TLS, FN, infection, AMS, mucositis, cardiac complication	CR	19-month follow up
35	Hamadah et al, 2017[25]	N/A	N/A	DLBCL	R-CHOP	25% reduction of CPA	3	Mucositis	CR	38-month follow up
36	Hamadah et al, 2017[25]	N/A	N/A	DLBCL	R-CHOP	25% reduction of CPA	6	Cardiac complication	CR	10-month follow up
37	Heggermont et al, 2017[30]	M	51	DLBCL	R-CHOP	N/A	N/A	N/A	improvement	CR after 3 courses of R-CHOP
38	Leite et al, 2017[31]	M	20	DLBCL	R-CHOP	N/A	N/A	N/A	improvement	alive
39	Palamuthusingam et al, 2017[32]	M	65	MCL	R-CHOP	Standard	5	N/A	CR	alive in CR at 12 months

(Continues)

TABLE 1 (Continued)

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome / time to follow up
40	South et al, 2018[33]	M	4	DLBCL	R-CHOP + IT MTX	N/A	N/A	Severe mucositis due to IT MTX	CR	alive in CR at 4 years
41	Morita et al, 2020[34]	M	55	DLBCL	R-CHOP	N/A	6	N/A	PD	proceeded to salvage chemotherapy due to PD
42	Fukuno et al, 2013[35]	M	60	FL	R-THP-COP	N/A	4	N/A	PR	relapsed and proceeded to salvage therapy
42	Fukuno et al, 2013[35]	M	60	FL relapse	R-THP-COP + R-CHOP + radiotherapy	N/A, CPA was excluded from THP-COP	THP-COP: 2 courses CHOP: 2 courses R: 8 courses	N/A	CR	relapsed and proceeded to ^{90}Y-ibritumomab tiuxetan therapy
43	Ochi et al, 2016[3]	M	79	DLBCL	R-THP-COP	RDI 36%	6	Neutropenia (grade 3), anemia (grade 3), infection (grade 3), heart failure (grade 3)	PR	alive at 31 months from diagnosis

Abbreviations: ^{90}Y, yttrium-90; AMS, altered mental status; BL, Burkitt lymphoma; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisolone; CHOP-E, CHOP + etoposide; CPA, cyclophosphamide; CR, complete response; CVP, cyclophosphamide + vincristine + prednisolone; DLBCL, diffuse large B-cell lymphoma; DXR, doxorubicin; F, female; FL, follicular lymphoma; FN, febrile neutropenia, IT, intrathecal; M, male; MCL, mantle cell lymphoma; MOF, multiple organ failure; MTX, methotrexate; MZL, marginal zone lymphoma; N/A, not available; NHL, non-Hodgkin lymphoma; PD, progressive disease; PN, peripheral neuropathy; PR, partial response, PSL, prednisolone; R, rituximab; RDI, relative dose intensity; THP-COP, pirarubicin + cyclophosphamide + vincristine + prednisolone; T-LGLL, T-cell large granular lymphocytic leukemia; TLS, tumor lysis syndrome; VCR, vincristine.

[a]Dexamethasone dose was confirmed to be 40 mg/body through personal communications.

TABLE 2 Various other regimens in hemodialysis patients

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome/time to follow up
44	Pascual et al., 1992[36]	M	53	CTCL	Chlorambucil + PSL	Chlorambucil: 0.1 mg/kg/day PSL: 1 mg/kg/day	N/A	N/A	CR	Alive in CR at 9 months
1	Jillella et al., 2002[10]	M	54	B-cell NHL	Chlorambucil + PSL	N/A	6	N/A	CR	Relapse at 20 months after treatment initiation
45	Karim et al., 2004[37]	M	75	MCL	Chlorambucil	5 mg/day	N/A	N/A	Improvement	Died of PD 14 months after treatment initiation
46	Karim et al., 2004[37]	M	68	MCL	Chlorambucil + PSL	Chlorambucil: 4 mg/day PSL: 1 mg/kg/day	N/A	N/A	Improvement	Died of pneumonia after 18 months
47	Niscola et al., 2009[38]	F	70	SMZL	R + chlorambucil	R: 375 mg/m^2 day 1 Chlorambucil: 6 mg/m^2 (day 1-10)	6	Mild fever and chills	CR	Alive in CR at 8 months after treatment initiation
48	Aw et al., 2018[39]	M	76	CLL	Ibrutinib	420 mg/day	14 days	N/A	PR	Alive in PR at nearly 2 years from treatment initiation
49	Yasuda et al., 2021[19]	M	73	MCL	Ibrutinib	560 mg/day	15 months	None	PR	Alive in PR at 15 months from treatment initiation
50	Balzer et al., 2016[40]	N/A	61	FL	BR	N/A	6	N/A	PR	DLBCL transformation at 17 months
51	Kudo et al., 2017[41]	M	58	LPL	BR	R: 375 mg/m^2 day 1 Bendamustine: 90 mg/m^2 day 2,3	6	Severe pneumonia	N/A	Died of pneumonia after course 6
52	Ettleson et al., 2019[42]	M	72	MCL	bendamustine + Ara-C	bendamustine 90 mg/m^2 day 1, 2 Ara-C 500 mg/m^2 day 1-3	1	N/A	Improvement	Alive
53	Murashima et al., 2009[43]	M	58	PCNSL	R + MTX + temozolomide	Course 1: MTX 3 g/m^2, Course 2: MTX 6 g/m^2, Course 3,4: MTX 4 g/m^2; R: N/A, temozolomide: N/A	4	Catheter infection	N/A	N/A

(Continues)

TABLE 2 (Continued)

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome/time to follow up
54	Mutsando et al., 2012[44]	F	52	PCNSL	R + MTX + DEX + IT Ara-C	R: 375 mg/m^2 MTX: 1 g/m^2 DEX: N/A IT Ara-C: 100 mg	2	Aortic valve endocarditis, arteriovenous fistula infection, urinary tract infection, neutropenia (grade 4), anemia, thrombocytopenia (grade 3), nausea, oral mucositis, mild transaminase elevation	CR	Died of CMV-related gastric ulcer perforation 4 months after course 2
41	Morita et al., 2020[34]	M	55	DLBCL	R-GDC	R: 375 mg/m^2 day 3 gemcitabine: 1000 mg/m^2 day 1,8 carboplatin: 125 mg/body day 1 DEX: 33 mg/body day 1-4	2	N/A	PD	Proceeded to salvage chemotherapy
50	Balzer et al., 2016[40]	N/A	61	DLBCL transformation	R-GemOx	R: N/A Gemcitabine: 1000 mg/m^2 day 1 Oxaliplatin: 50 mg/m^2 day 1	3	N/A	PR	N/A
55	Pöschl et al., 1993[45]	M	8	BL	PSL + CPA + MTX + DXR + Ara-C	PSL: 30 mg/body day 1-14 CPA: 145 mg/m^2 day 7-12 CPA: 230 mg/m^2 day 13-15 MTX: 25 mg/m^2 day 42 MTX: 16 mg/m^2 day 84 DXR: 2 mg/m^2 day 18, 19, 53, 54, 96, 97 Ara-C: 100 mg/m^2 for 7 days on week 4	1	Fever	PD	Died of PD 5 months after treatment initiation

(Continues)

TABLE 2 (Continued)

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome/time to follow up
56	Radeski et al., 2011[46]	F	48	MCL	Ara-C	1 g/m^2 (capped at 2 g/ body) day 1,2	3	No neurotoxicity and no other unexpected toxicities	PR	Alive
41	Morita et al., 2020[34]	M	55	DLBCL	CHASER	R: 375 mg/m^2 day 1 CPA: 600 mg/m^2 day 2 ETP: 50 mg/m^2 day 2-4 Ara-C: 1000 mg/m^2 day 4,5 DEX: 33 mg/body day 2,4,5	2	N/A	PR	Proceeded to ASCT
57	Hamadah et al., 2017[25]	N/A	N/A	DLBCL	Modified ProMACE/ CytaBOM	50% reduction of CPA; BLM, VCR, and MTX omitted	1	TLS, infection, AMS	N/A	1-month follow up
58	Boros et al., 1992[47]	F	71	NHL	Mitoxantrone + CPA + VCR + hydrocortisone	Mitoxantrone: 10 mg/ m^2 CPA: 650 mg/m^2 VCR: 1.5 mg/body, Hydrocortisone: N/A	1	Pseudomonas aeruginosa sepsis (grade 5), leukocytopenia (grade 4)	N/A	Died of sepsis on day 11 after treatment initiation
59	Baldus et al., 1996[48]	F	72	B-cell NHL	Mitoxantrone + prednimustine	Mitoxantrone: 8 mg/ m^2 day 1 for course 1-3; 8 mg/m^2 day 1,2 for course 4 Prednimustine: 100 mg/m^2 day 1-5 for course 1-4	4	Leukocytopenia (grade 2), thrombocytopenia (grade 3)	PR	Died of sepsis 7 months after diagnosis
60	Ostronoff et al., 2006[49]	F	58	NHL	R + liposomal daunorubicin	R: 100 mg/body/day for 6 days liposomal daunorubicin: N/A	1	No infusion related events	N/A	Alive at 36 months after auto-PBSCT
61	Ostronoff et al., 2006[49]	M	76	NHL	R + liposomal daunorubicin	R: 100 mg/body/day for 7 days liposomal daunorubicin: 50 mg/body for 2 days	1	No infusion related events	N/A	Died of sepsis during subsequent CHOP therapy

(Continues)

TABLE 2 (Continued)

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome/time to follow up
42	Fukuno et al., 2013[35]	M	60	FL	^{90}Y-ibritumomab tiuxetan	R: 250 mg/m^2 (pretreatment) ^{90}Y-ibritumomab tiuxetan: 11.1 MBq/kg	1	Neutropenia (grade 4), lymphopenia (grade 4), thrombocytopenia (grade 4), non-hematological toxicities (grade 2 or lower)	CR	Relapse after 18 months
62	Yoshihara et al., 2014[50]	F	83	ATLL	Mogamulizumab	1 mg/kg	1	No major adverse events	N/A	Died of PD 10 months after diagnosis
63	Nanni et al., 2019[51]	M	44	ALK-negative sALCL	brentuximab vedotin	1.2 mg/kg	16	PN (grade 1), phlebitis	CR	Alive in CR at 1 year

Abbreviations: ^{90}Y, Yttrium-90; AMS, altered mental status; Ara-C, cytarabine; ASCT, autologous stem cell transplantation; ATLL, adult T-cell leukemia / lymphoma; BL, Burkitt lymphoma; BLM, bleomycin; CHASER, rituximab + cyclophosphamide + cytarabine + etoposide + dexamethasone; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DXR, doxorubicin; ETP, etoposide; F, female; FL, follicular lymphoma; GemOx, gemcitabine + oxaliplatin; GDC, gemcitabine + dexamethasone + carboplatin; IT, intrathecal; LPL, lymphoplasmacytic lymphoma; M, male; MCL, mantle cell lymphoma; MTX, methotrexate; N/A, not available; NHL, non-Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; PD, progressive disease; PN, peripheral neuropathy; PR, partial response, ProMACE / CytaBOM, prednisolone + methotrexate + doxorubicin + cyclophosphamide + etoposide / cytarabine + bleomycin + vincristine + methotrexate; PSL, prednisolone; R, rituximab; SMZL, splenic marginal zone lymphoma; sALCL, systemic anaplastic large cell lymphoma; TLS, tumor lysis syndrome; VCR, vincristine.

TABLE 3 Stem cell transplantation in hemodialysis patients

Case number	Reporter, year	Sex	Age	Disease	Treatment	Dose administrations/ modifications	Number of chemotherapy courses under HD	Adverse events	Response	Outcome / time to follow up
64	Ullery et al, 2000[52]	M	47	DLBCL	BU + CPA (ASCT conditioning)	Busulfan: 0.17-1.0 mg/kg 4 times/day CPA: 50 mg/kg and 100 mg/kg on different days	Busulfan: total 19 doses CPA: administered on 2 days	N/A	CR	Died unrelated to DLBCL at 3 years
65	Tendas et al, 2009[53]	M	69	MCL	FLU + MEL (ASCT conditioning)	FLU: 6 mg/m^2 days 1-4 MEL: 100 mg/m^2 day 5	1	FN, mucositis	CR	Alive in CR at 16 months post-ASCT
41	Morita et al, 2020[34]	M	55	DLBCL	MEL + BU (ASCT conditioning)	MEL: 100 mg/m^2 day -2 BU: 0.8 mg/kg day -10; 3.1 mg/kg days -6,-5, -4, -3	1	FN (grade 3), diarrhea (grade 3)	CR	Died 2 months after ASCT
66	Shadman et al, 2017[54]	F	52	FL	2 Gy TBI (allo-HSCT conditioning)	Cyclosporin: monitored to achieve therapeutic blood levels of 120-360 ng/mL; mycophenolate mofetil: standard dose (GVHD prophylaxis)	0	N/A	N/A	Died of bleeding during heart surgery 82 months after transplant

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; BU, busulfan; CPA, cyclophosphamide; CR, complete response; DLBCL, diffuse large B-cell lymphoma; F, female; FL, follicular lymphoma; FLU, fludarabine; FN, febrile neutropenia; GVHD, graft-versus-host disease; M, male; MCL, mantle cell lymphoma; MEL, melphalan; N/A, not available; NHL, non-Hodgkin lymphoma; TBI, total body irradiation.

TABLE 4 Recommendations on drug administration in hemodialysis patients

Drug	Dose modifications	Timing of administration
Bendamustine[56]	Standard dose	After HD
Carboplatin[4]	AUC × 25	After HD
Chlorambucil[38,55]	Standard dose	After HD
Cisplatin[4]	50% reduction	After HD
Cyclophosphamide[4]	25% reduction	After HD
Cytarabine[46]	N/A	Infusion completion should be timed 4-5 h before HD
Doxorubicin[4]	Standard dose	After HD
Etoposide[4]	50% reduction	Before or after HD
Gemcitabine[4,57]	Standard dose	6-12 h before HD
Ibrutinib[19,39]	Standard dose?	After HD
Ifosfamide[5,9,58]	Administration to HD patients is controversial	
Melphalan[59,60]	30%-50% reduction	After HD
Methotrexate[4,43,44]	Administration to HD patients is controversial	
Oxaliplatin[4]	30% reduction	After HD
Rituximab[10,11]	Standard dose	Before or after HD
Vincristine[3,25]	Standard dose	After HD

Note: Superscripts show the number of the reference that is the source of the recommendation.
Abbreviations: AUC, area under the concentration-time curve; HD, hemodialysis; N/A, not available.

4.2 | Chlorambucil

Chlorambucil is an orally administered alkylating agent that is mostly metabolized by the liver, and renal excretion is reported to be extremely low,[55] therefore the pharmacokinetics of chlorambucil are considered to be basically not influenced by renal deficiency.[38] Five NHL patients on HD have been reported to be treated with chlorambucil (cases 1 and 44-47), of which one was monotherapy, three were treated with PSL, and one was treated with concomitant rituximab therapy.[10,36-38] Although adverse events were not specifically commented on in four of the five patients, chlorambucil seemed to be tolerated well overall.

4.3 | Ibrutinib

Ibrutinib is an oral BTK inhibitor with minimal renal excretion.[65] Ibrutinib peak plasma concentrations are reached at 1-2 h after oral intake, and the terminal half-life is reported to be 4-8 h. Despite rapid absorption and elimination, BTK occupancy by ibrutinib is known to continue for over 24 h. Drug removal rates of ibrutinib through HD are unknown, and thus ibrutinib should be administered after HD on days where it is planned.[19] There are only reports of two patients treated with ibrutinib under HD (cases 48 and 49). Ibrutinib was administered for 2 weeks at 420 mg/day for chronic lymphocytic leukemia in one patient and for 15 months at 560 mg/day for mantle cell lymphoma in the other patient. Both patients tolerated ibrutinib well.[19,39] Ibrutinib increases risk of bleeding through inhibition of BTK and tyrosine kinase expressed in hepatocellular carcinoma kinase, but bleeding events were not reported in cases 48 and 49. Dose reductions of ibrutinib are most probably not necessary in HD patients, but accumulation of further evidence is necessary to make firm recommendations.

4.4 | Bendamustine

Bendamustine is a purine analog/alkylator hybrid drug that is primarily metabolized in the liver, with limited renal elimination.[42] Removal rates of bendamustine through HD are unknown and administration of the drug should be after HD. However, bendamustine has high protein binding rates and therefore removal by HD can be expected to be limited.[42] Bendamustine 60 mg/m^2 on two consecutive days along with bortezomib and PSL administration was reported to be well tolerated in multiple myeloma patients with renal failure, including patients on HD, and bendamustine was administered post-HD in this study.[56] Another study of 12 multiple myeloma patients with severe renal impairment, including five HD patients undergoing two consecutive days of bendamustine 120 mg/m^2 at 4-week intervals, demonstrated that although higher frequencies of leukocytopenia and thrombocytopenia were observed in patients with renal insufficiency, other toxicities were comparable with patients with normal kidney function.[56] Thus, dose reductions of bendamustine are not mandatory

in HD patients. There are three case reports of NHL patients on HD treated with bendamustine (cases 50-52), two as part of the BR regimen and one in conjunction with Ara-C. Two patients were treated with a bendamustine dose of 90 mg/m^2 on two consecutive days and the dose was not elucidated in one patient. Adverse events were not clarified in all three patients, but one patient died of severe pneumonia after the sixth course of BR, and the other two patients were alive at time of reporting. [40-42] Bendamustine is a drug known for its prolonged immune suppression, and special caution is necessary when administrating the drug to HD patients because they are prone to infections to begin with.

4.5 | Methotrexate

MTX is an antimetabolite that constitutes the backbone therapy for NHL involving the CNS. MTX metabolism is minimal in humans and 90% is excreted unchanged in urine. HD has limited effectiveness in reducing plasma MTX because of its moderate plasma protein binding rate of 50% and large volume of distribution of 0.76 L/kg.[44] Even low-dose MTX administration in patients with ESRD has been reported to cause severe complications due to delayed elimination and drug accumulation, and MTX therapy in ESRD patients is controversial.[66,67] Experience with high-dose MTX in HD patients is even more limited, and there are only two reports of NHL patients treated with high-dose MTX (cases 53 and 54).[43,44] Case 53 was treated with a 4-h MTX infusion of 3-6 g/m^2 followed by daily 6-h HD sessions starting within 24 h after MTX infusion.[43] Case 54 was treated with a 2-h MTX infusion of 1 g/m^2 followed by five daily 4-9-h HD sessions commencing 1 h following completion of MTX infusion.[44] Case 53 was treated with concomitant rituximab and temozolomide, and case 54 with rituximab, dexamethasone, and intrathecal Ara-C. Both cases achieved MTX blood levels under 0.1 μmol/L within 3-4 days through appropriate drug removal by daily HD support. While case 53 did not show signs of MTX toxicity, case 54 suffered from multiple complications, of which some may not be directly related to MTX administration. Janus et al have proposed a 75% dose reduction and administration after HD for MTX,[4] but MTX is likely to be used for CNS lymphoma when treating NHL, and such low doses will not penetrate to the CNS. Although MTX administration to HD patients cannot be recommended at this point, high-dose MTX followed by daily HD sessions to purposefully extract MTX as was done with cases 53 and 54 might be a more rational strategy than dose reduction when MTX is mandatory.

4.6 | Cisplatin, carboplatin, and oxaliplatin

Cisplatin, carboplatin, and oxaliplatin are platinum compounds that are frequently incorporated as part of multiagent chemotherapy for NHL. Cisplatin, carboplatin, and oxaliplatin are predominantly eliminated by the kidneys.[4,5,68]

Cisplatin has been administered to HD patients with lung cancer at doses ranging from 40 to 80 mg/m^2, and toxicities were feasible overall.[69] However, there are no reports of cisplatin administration in NHL patients on HD. The optimal timing of cisplatin administration remains obscure, with some investigators administering cisplatin before HD,[69,70] while Janus et al recommend administration after HD due to the fact that cisplatin is dialyzable.[4] Janus et al also recommend an initial cisplatin dose reduction of 50%, translating to an actual administration of 25-50 mg/m^2 every 3-6 weeks.

Carboplatin is a less toxic analogue of cisplatin, and clearance of the drug has been reported to be linearly related to GFR. Unlike most other chemotherapeutics in which body surface area (BSA) is utilized for calculating dosage, the Calvert formula is widely accepted for deciding carboplatin dosing. The Calvert formula calculates the necessary carboplatin dose to achieve a particular AUC, and the equation is as follows: dose (mg) = target AUC (mg/mL × min) × [GFR (mL/min) + 25].[68] Because the GFR in chronic HD patients is equal to or close to 0 after an HD session, it has been proposed to administer carboplatin after HD by inserting a value of 0 as the GFR in the Calvert formula, and thereby defining necessary carboplatin dosage in the HD patient as target AUC × 25. Carboplatin has been administered at 125 mg/body as part of the R-GDC regimen (rituximab + gemcitabine + dexamethasone + carboplatin) in one NHL patient on HD (case 41), in which information on toxicities was not specified.[34]

Oxaliplatin is a relatively new platinum compound, and there are only a few case reports of HD patients undergoing treatment with oxaliplatin, mostly patients with colon cancer. Four colon cancer patients on HD were treated with oxaliplatin doses ranging from 40 to 85 mg/m^2.[71] Oxaliplatin was administered before HD in these case reports, but because oxaliplatin is removed through HD, it has been proposed that administration may be best done after or on non-HD days by some investigators.[4,5] There is only one report of an HD patient with NHL treated with oxaliplatin (case 50), in which oxaliplatin was administered as part of the R-GemOx regimen (rituximab + gemcitabine + oxaliplatin). In this report, oxaliplatin was reduced to 50%, translating to a dose of 50 mg/m^2, and HD was carried out for five consecutive days after administration of oxaliplatin by which time the authors concluded that serum platinum levels were controlled at non-toxic levels.[40] The optimal dose and administration timing of oxaliplatin in HD patients has not been clarified, and while not recommending oxaliplatin administration in HD patients unless mandatory, Janus et al have suggested a 30% dose reduction for HD patients.[4]

4.7 | Cytarabine

Cytarabine, otherwise known as cytosine arabinoside (Ara-C), is a nucleoside analog that is rapidly converted through deamination to an inactive but most probably neurotoxic metabolite, uracil arabinoside (Ara-U), and as a result plasma Ara-C levels are found to be low after a mere 2 h.[46] Therefore, Ara-U and not Ara-C becomes the main concern as with toxicities. There are four reports of systemic Ara-C administration in NHL patients on HD,

one as Ara-C monotherapy, one in conjunction with bendamustine, and two as part of multiagent chemotherapy (cases 41, 52, 55, and 56).[34,42,45,46] Pharmacokinetic studies were carried out in the Ara-C monotherapy report by Radeski et al (case 56) and they demonstrated that 39%-52% of Ara-U was removed by HD sessions. They performed 2-h infusions of Ara-C 1 g/m^2 (capped at 2 g/body) on two consecutive days both followed by 4-h HD sessions starting 3.5 and 2 h after completion of Ara-C infusion, and neurotoxicity and other unexpected toxicities were absent. Radeski et al suggested that HD sessions should be started about 4-5 h after completion of Ara-C infusions to maximize Ara-C efficacy while preventing Ara-U toxicity.[46]

4.8 | Gemcitabine

Gemcitabine is a nucleoside analog that is rapidly deaminated to a noncytotoxic metabolite, 2',2'-difluorodeoxyuridine (dFdU). Renal elimination of gemcitabine as a parent drug is less than 10%, but dFdU is reported to be excreted in urine at rates of 29%-86% within the first 24 h after administration.[4,72] Although the pharmacokinetics of gemcitabine, including terminal half-life and AUC, were similar in an ESRD patient on HD compared to patients with normal renal function, terminal half-life prolongation of 5- to 10-fold and an AUC increase of dFdU was observed.[57] Although the dialysability of gemcitabine is unknown, dFdU is reported to be removed by HD. Therefore, it is recommended to initiate HD sessions 6-12 h after gemcitabine administration to minimize the potential side effects of dFdU. In previous reports of HD patients receiving gemcitabine, toxicities were similar compared to patients with normal renal function, and dose reductions of gemcitabine are generally not recommended.[4,5] Gemcitabine has been administered at 1000 mg/m^2 in two NHL patients on HD (cases 41 and 50), in which information on adverse events was not commented on.[34,40]

4.9 | Etoposide

Etoposide is a topoisomerase-II inhibitor of which approximately 40% is excreted by the kidneys.[73] Some studies have reported that pharmacokinetic parameters of etoposide were similar between HD patients and patients with normal renal function,[69,74] whereas others have demonstrated an AUC rise and prolonged half-life in patients with renal insufficiency, including patients on HD.[4] Etoposide dose reductions of 50%, translating to actual dosing of 25-75 mg/m^2, have been proposed by investigators for patients on HD.[4] Etoposide is not removed by HD and administration can be done before or after HD sessions.[75] Three NHL patients on HD have been treated with etoposide (cases 21, 22, and 57), two in conjunction with CHOP, and one as part of a modified proMACE/CytaBOM regimen (prednisolone + methotrexate + doxorubicin + cyclophosphamide + etoposide/cytarabine + bleomycin + vincristine + methotrexate).[25] Etoposide dosage was not clarified in these patients. All patients experienced multiple adverse events, including infections, but because etoposide was administered as part of multiagent chemotherapy in all patients, it is difficult to assess to what extent etoposide contributed to these adverse events.

4.10 | Ifosfamide

Ifosfamide is an alkylating agent frequently used as part of multiagent chemotherapy for NHL. However, there are no reports of ifosfamide administration in NHL patients on HD. Ifosfamide is predominantly metabolized in the liver and is transformed to an active phosphoramide mustard, but also gives birth to the urotoxic metabolite acrolein, and the nephrotoxic and neurotoxic metabolite chloroacetaldehyde.[5] Carlson et al carried out ifosfamide pharmacokinetic studies in a child with Wilms' tumor, and reported HD extraction rates of 87% and 77% for ifosfamide and chloroacetaldehyde, respectively. In this study, neurotoxicity was observed within hours after ifosfamide administration, which improved rapidly after HD. Latcha et al reported three sarcoma HD patients treated with 1.5-4.0 mg/m^2 of ifosfamide which was administered on a single day or divided between two separate days, and they concluded that ifosfamide treatment was feasible.[58] However, other investigators contraindicate or look upon its use as controversial in HD patients, and definite recommendations cannot be made.[5,9]

4.11 | ^{90}Y-ibritumomab tiuxetan, mogamulizumab, and brentuximab vedotin

Experience with antibody therapy other than rituximab in HD patients is scarce.

^{90}Y-ibritumomab tiuxetan (IDEC-Y2B8) is an anti-CD20 radioimmunoconjugate in which the monoclonal murine antibody ibritumomab is radiolabeled by yttrium-90. IDEC-Y2B8 has a large molecular mass of 148 kDa, which is similar to the molecular mass of rituximab (145 kDa), and although pharmacokinetic studies in HD patients are lacking, removal through HD is highly unlikely.[35] There is one report of an NHL patient on HD treated with IDEC-Y2B8 (case 42), in which no critical adverse events were observed and the patient achieved a complete response.[35]

Mogamulizumab is a defucosylated humanized anti-CCR4 antibody used for treatment of T-cell NHLs. There is one report of mogamulizumab treatment in an NHL patient on HD (case 62), in which plasma concentrations of mogamulizumab were studied and found to be comparable before and after HD, suggesting that the drug is not removed by HD. No major adverse events were observed, and the authors concluded that mogamulizumab therapy in HD patients may be safe.[50]

BV is an anti-CD30 antibody covalently linked to MMAE. In a phase I trial, patients with severe renal impairment (creatinine clearance <30 mL/min) were found to have a 1.9-fold increase of MMAE exposure,[76] and in the single case report of BV administered to a

NHL patient on HD (case 63), BV was administered at 1.2 mg/kg instead of the standard dose of 1.8 mg/kg. There is no information on the optimal timing of BV administration as to HD sessions, but in this case report HD was commenced approximately 24 h after BV infusion. No exceptional toxicities were observed and the patient achieved a complete response.[51]

4.12 | Autologous and allogeneic hematopoietic stem cell transplantation

Experience with HSCT in NHL patients on HD is extremely limited. In the three reports of autologous HSCT (cases 41, 64, and 65), conditioning regimens consisted of MEL + BU, FLU + MEL, and BU + CPA.[34,52,53] In a study of multiple myeloma patients on HD undergoing autologous HSCT, patients receiving 200 and 140 mg/m^2 of MEL as conditioning regimens were compared, and the former group showed significantly higher rates of MEL toxicities while efficacy did not differ between the two groups. MEL dose reductions of 30%-50% have been recommended in multiple myeloma patients with ESRD and may be of reference also for treating NHL patients on HD.[59,60] BU is mainly eliminated by the liver and renal elimination is limited. BU is efficiently removed by HD, but a standard 4-h HD has been reported to not significantly alter BU exposure when orally administered every 6 h.[52] Another group reported experience with intravenous administration of BU by first giving a test dose and estimating the dose required to achieve the target AUC through pharmacokinetic analysis.[34] Up to 60% of the primary metabolite of FLU is eliminated by the kidneys, but because the drug is adequately removed through HD, there are case reports in which patients were successfully treated with dose reductions and daily HD sessions following FLU administration.[77,78] FLU dose reductions of 20% have been proposed by some reporters.[77]

There is only one report of an NHL patient on HD undergoing allogeneic HSCT (case 66), in which the conditioning regimen was 2 Gy total body irradiation (TBI) followed by graft-versus-host disease (GVHD) prophylaxis with cyclosporin and MMF. The actual dose of cyclosporin administered was not mentioned, but dosing was adjusted to achieve a therapeutic level between 120 and 360 ng/mL. MMF was given as the standard dose.[54]

5 | CONCLUDING REMARKS

Chemotherapy for the HD patient is a challenging situation. Drug selection, dosing, and HD timing must be carefully planned depending on the distinct pharmacological traits of individual drugs. For drugs where pharmacological information is lacking, reports of actual drug administration and outcomes in HD patients may be of precious reference. HD technology constantly evolves, and information from older reports of drug administration in HD patients may not be valid under current practice. Constant updating and accumulation of experience with new drugs and HD technologies is necessary.

CONFLICT OF INTEREST

NK received grants from Meiji Seika Pharma, Shire/Takeda, Chugai Pharmaceutical, Kyowa Kirin, and Bristol-Meyer Squibb. NK received personal fees from Shire/Takeda. All other authors declare no conflict of interest.

ORCID

Hajime Yasuda https://orcid.org/0000-0002-2896-7737
Norio Komatsu https://orcid.org/0000-0003-1880-9126

REFERENCES

1. Hortlund M, Arroyo Muhr LS, Storm H, Engholm G, Dillner J, Bzhalava D. Cancer risks after solid organ transplantation and after long-term dialysis. *Int J Cancer*. 2017;140(5):1091-1101.
2. Alkhunaizi AM, Daabil RA, Dawamneh MF. Acute kidney injury secondary to lymphomatous infiltration and the role of kidney biopsy. *Saudi Med J*. 2008;29(12):1808-1810.
3. Ochi Y, Hiramoto N, Ono Y, et al. Tolerability and efficacy of rituximab-containing immunochemotherapy in patients with B-cell non-Hodgkin lymphoma receiving hemodialysis. *Leuk Lymphoma*. 2016;57(8):1945-1948.
4. Janus N, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. *Ann Oncol*. 2010;21(7):1395-1403.
5. Pedrazzoli P, Silvestris N, Santoro A, et al. Management of patients with end-stage renal disease undergoing chemotherapy: recommendations of the Associazione Italiana di Oncologia Medica (AIOM) and the Societa Italiana di Nefrologia (SIN). *ESMO Open*. 2017;2(3):e000167.
6. Lin CJ, Chen HH, Hsieh RK, Chen YC, Wu CJ. Acute tumor lysis syndrome in a hemodialysis patient with diffuse large B cell lymphoma. *Med Oncol*. 2009;26(1):93-95.
7. Gotta V, Dao K, Rodieux F, Buclin T, Livio F, Pfister M. Guidance to develop individual dose recommendations for patients on chronic hemodialysis. *Expert Rev Clin Pharmacol*. 2017;10(7):737-752.
8. Mueller BA, Smoyer WE. Challenges in developing evidence-based drug dosing guidelines for adults and children receiving renal replacement therapy. *Clin Pharmacol Ther*. 2009;86(5):479-482.
9. Tomita M, Aoki Y, Tanaka K. Effect of haemodialysis on the pharmacokinetics of antineoplastic drugs. *Clin Pharmacokinet*. 2004;43(8):515-527.
10. Jillella AP, Dainer PM, Kallab AM, Ustun C. Treatment of a patient with end-stage renal disease with Rituximab: pharmacokinetic evaluation suggests Rituximab is not eliminated by hemodialysis. *Am J Hematol*. 2002;71(3):219-222.
11. Morita Y, Matsuda M, Yamaguchi T, et al. Efficacy of rituximab monotherapy for an elderly hemodialysis patient with primary cardiac lymphoma. *Intern Med*. 2010;49(19):2163-2166.
12. Ablin A, Stephens BG, Hirata T, Wilson K, Williams HE. Nephropathy, xanthinuria, and orotic aciduria complicating Burkitt's lymphoma treated with chemotherapy and allopurinol. *Metabolism*. 1972;21(8):771-778.
13. Milsted RA, Jarman M. Haemodialysis during cyclophosphamide treatment. *Br Med J*. 1978;1(6116):820-821.
14. Gianviti A, Boldrini R, Bosman C, Rizzoni G. Chronic renal failure due to kidney infiltration by Burkitt type lymphoma. *Pediatr Nephrol*. 1989;3(4):448-450.
15. Ozaltin F, Yalcin B, Orhan D, et al. An unusual cause of acute renal failure: renal lymphoma. *Pediatr Nephrol*. 2004;19(8):912-914.

16. Christopoulos PD, Katsoudas S, Androulaki A, Nakopoulou L, Economopoulos T, Vlahakos DV. T-cell large granular lymphocyte leukemia presenting as end-stage renal disease: the diagnostic role of flow-cytometric and clonality analysis of the urine sediment. *Clin Nephrol*. 2009;71(2):198-202.
17. Li Cavoli G, Passantino R, Ferrantelli A, Rotolo U. Kidney infiltration due to malignant lymphoma. *Clin Kidney J*. 2012;5(4):369-371.
18. Miyata KN, Siddiqi NA, Kiss LP, Harbord NB, Winchester JF. Antineutrophil cytoplasmic antibody-positive pauci-immune glomerulonephritis associated with mantle cell lymphoma. *Clin Nephrol Case Stud*. 2017;5:9-15.
19. Yasuda H, Tsukune Y, Inano T, Mori Y, Ota Y, Komatsu N. Successful long-term ibrutinib treatment in a hemodialysis patient with leukemic nonnodal mantle cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2021;21(2):e176-e178.
20. Weng SC, Shu KH, Wen MC, et al. Malignant lymphoma of the kidney mimicking rapid progressive glomerulonephritis. *Clin Nephrol*. 2010;74(6):480-484.
21. Gangireddy M, Shrimanker I, Nookala VK, Peroutka KA. Spontaneous tumor lysis syndrome in diffuse large B-cell lymphoma: Early diagnosis and management. *Cureus*. 2019;11(5):e4679.
22. Paganelli E, Arisi L, Ferrari ME, Olivetti G, Tedeschi F. Primary non-Hodgkin's lymphoma of the kidney. *Haematologica*. 1989;74(3):301-304.
23. Agha-Razii M, Amyot SL, Pichette V, Cardinal J, Ouimet D, Leblanc M. Continuous veno-venous hemodiafiltration for the treatment of spontaneous tumor lysis syndrome complicated by acute renal failure and severe hyperuricemia. *Clin Nephrol*. 2000;54(1):59-63.
24. Peddi S, Ram R, Kataru SR, et al. Acute renal failure in a patient with mantle cell lymphoma. *Hemodial Int*. 2015;19(3):E12-E15.
25. Hamadah AM, Thanarajasingam G, Gharaibeh KA, Finnes HD, Thompson CA, Leung N. Efficacy, safety, and dose adjustment of cyclophosphamide in lymphoma patients requiring hemodialysis. *Leuk Lymphoma*. 2017;58(2):457-460.
26. de Barros PL, Todaro J, Karnakis T, et al. Treatment of a frail older patient with diffuse large B-cell lymphoma on maintenance dialysis: attenuated immunochemotherapy and adapted care plan. *Case Rep Oncol*. 2013;6(1):197-203.
27. Feldmann G, Nattermann J, Gerhardt T, Nähle CP, Spengler U, Woitas R. Partial remission of a newly diagnosed diffuse large B-cell Non-Hodgkin's lymphoma in a hemodialysis patient after administration of immuno-chemotherapy with rituximab-CHOP. *Int J Lab Hematol*. 2007;29(6):469-473.
28. Jorge S, Lopes JA, Goncalves S, Esteves G, Alves do Carmo J. Acute kidney injury requiring dialysis: a very unusual presentation of non-Hodgkin's lymphoma. *NDT Plus*. 2010;3(4):338-340.
29. Kawano N, Yokota-Ikeda N, Kawano S, et al. Successful treatment of non-Hodgkin's lymphoma with rituximab and dose-adjusted CHOP therapy in a patient with concomitant end-stage renal disease requiring haemodialysis. *NDT Plus*. 2011;4(3):186-189.
30. Heggermont WA, Verhoef G, Evenepoel P, et al. Clinical case report: a rare cause of acute kidney failure - tissue is the issue. *Acta Clin Belg*. 2017;72(3):201-204.
31. Leite TT, Libório AB, Silva Junior GB, Daher EF. Oliguric acute kidney injury as initial presentation of renal non-Hodgkin's lymphoma infiltration. *Saudi J Kidney Dis Transpl*. 2017;28(3):645-647.
32. Palamuthusingam D, Mantha M, Oliver K, Bavishi K, Dheda S. Mini review: A unique case of crescentic C3 glomerulonephritis. *Nephrology*. 2017;22(3):261-264.
33. South AM. Primary renal diffuse large B-Cell lymphoma causing haemodialysis-dependent nephromegaly in a child. *BMJ Case Rep*. 2018;bcr2018226328. https://doi.org/10.1136/bcr-2018-226328.
34. Morita K, Ashizawa M, Toda Y, et al. Salvage chemotherapy followed by autologous stem-cell transplantation using targeted Busulfan for refractory diffuse large B-cell lymphoma with dialysis-dependent end-stage renal disease. *Clin Lymphoma Myeloma Leuk*. 2020;20(2):e92-e96.
35. Fukuno K, Tsurumi H, Yamada T, Iida T, Takahashi T, Moriwaki H. Radioimmunotherapy with 90Y-ibritumomab tiuxetan for a hemodialysis patient with relapsed follicular lymphoma. *Leuk Lymphoma*. 2013;54(12):2731-2733.
36. Pascual J, Torrelo A, Teruel JL, Bellas C, Marcén R, Ortuño J. Cutaneous T cell lymphomas after renal transplantation. *Transplantation*. 1992;53(5):1143-1145.
37. Karim M, Hill P, Pillai G, Gatter K, Davies DR, Winearls CG. Proliferative glomerulonephritis associated with mantle cell lymphoma–natural history and effect of treatment in 2 cases. *Clin Nephrol*. 2004;61(6):422-428.
38. Niscola P, Palumbo R, Scaramucci L, et al. Successful treatment with a rituximab-based regimen of a splenic marginal zone lymphoma with villous lymphocytes in a very frail patient on maintenance dialysis. *Cancer Chemother Pharmacol*. 2009;63(4):759-760.
39. Aw A, Hellman JM, Birner A, Davids MS. A complex case of ibrutinib treatment for a CLL patient on haemodialysis. *Br J Haematol*. 2018;181(6):854-857.
40. Balzer MS, Eggers H, Heuser M, Reising A, Bertram A. Oxaliplatin pharmacokinetics on hemodialysis in a patient with diffuse large B cell lymphoma. *Ann Hematol*. 2016;95(4):649-650.
41. Kudo N, Usui M, Nakabo Y, et al. Waldenstrom's macroglobulinemia: A report of two cases, one with severe retinopathy and one with renal failure. *Case Rep Hematol*. 2017;2017:3732902.
42. Ettleson M, Bongers KS, Vitale K, Perissinotti AJ, Phillips T, Marini BL. Successful use of cytarabine and bendamustine in a patient with mantle cell lymphoma and acute renal failure using intermittent hemodialysis: A case report. *J Oncol Pharm Pract*. 2019;25(3):731-734.
43. Murashima M, Adamski J, Milone MC, Shaw L, Tsai DE, Bloom RD. Methotrexate clearance by high-flux hemodialysis and peritoneal dialysis: a case report. *Am J Kidney Dis*. 2009;53(5):871-874.
44. Mutsando H, Fahim M, Gill DS, et al. High dose methotrexate and extended hours high-flux hemodialysis for the treatment of primary central nervous system lymphoma in a patient with end stage renal disease. *Am J Blood Res*. 2012;2(1):66-70.
45. Pöschl JM, Klaus G, Querfeld U, Ludwig R, Mehls O. Chemotherapy with cytosine arabinoside in a child with Burkitt's lymphoma on maintenance hemodialysis and hemofiltration. *Ann Hematol*. 1993;67(1):37-39.
46. Radeski D, Cull GM, Cain M, Hackett LP, Ilett KF. Effective clearance of Ara-U the major metabolite of cytosine arabinoside (Ara-C) by hemodialysis in a patient with lymphoma and end-stage renal failure. *Cancer Chemother Pharmacol*. 2011;67(4):765-768.
47. Boros L, Cacek T, Pine RB, Battaglia AC. Distribution characteristics of mitoxantrone in a patient undergoing hemodialysis. *Cancer Chemother Pharmacol*. 1992;31(1):57-60.
48. Baldus M, Klooker P, Kress S, Waldherr R, Möller P, Brass H. Primary bilateral renal centrocytic non-Hodgkin's lymphoma as a cause of renal failure. *Nephron*. 1996;73(1):86-90.
49. Ostronoff F, Ostronoff M, Florêncio R, et al. Safety of fractionated dose of rituximab in renal failure patients receiving hemodialysis. *Leuk Lymphoma*. 2006;47(4):757-759.
50. Yoshihara M, Kubota Y, Fukuda M, et al. Mogamulizumab treatment in a hemodialysis patient with adult T-cell leukemia/lymphoma. *Turk J Haematol*. 2014;31(4):424-425.
51. Nanni L, Pellegrini C, Stefoni V, Argnani L, Cavo M, Zinzani PL. Successful employment of brentuximab vedotin in a patient undergoing hemodialysis: the first real-life experience. *Clin Lymphoma Myeloma Leuk*. 2019;19(11):e595-e596.
52. Ullery LL, Gibbs JP, Ames GW, Senecal FM, Slattery JT. Busulfan clearance in renal failure and hemodialysis. *Bone Marrow Transplant*. 2000;25(2):201-203.

53. Tendas A, Cupelli L, Dentamaro T, et al. Feasibility of a dose-adjusted fludarabine-melphalan conditioning prior autologous stem cell transplantation in a dialysis-dependent patient with mantle cell lymphoma. *Ann Hematol*. 2009;88(3):285-286.
54. Shadman M, Hingorani S, Lanum SA, et al. Allogeneic hematopoietic cell transplant for patients with end stage renal disease requiring dialysis – a single institution experience. *Leuk Lymphoma*. 2017;58(3):740-742.
55. Alberts DS, Chang SY, Chen HS, Larcom BJ, Evans TL. Comparative pharmacokinetics of chlorambucil and melphalan in man. *Recent Results Cancer Res*. 1980;74:124-131.
56. Pönisch W, Moll B, Bourgeois M, et al. Bendamustine and prednisone in combination with bortezomib (BPV) in the treatment of patients with relapsed or refractory multiple myeloma and light chain-induced renal failure. *J Cancer Res Clin Oncol*. 2013;139(11):1937-1946.
57. Kiani A, Köhne CH, Franz T, et al. Pharmacokinetics of gemcitabine in a patient with end-stage renal disease: effective clearance of its main metabolite by standard hemodialysis treatment. *Cancer Chemother Pharmacol*. 2003;51(3):266-270.
58. Latcha S, Maki RG, Schwartz GK, Flombaum CD. Ifosfamide may be safely used in patients with end stage renal disease on hemodialysis. *Sarcoma*. 2009;2009:575629.
59. Badros A, Barlogie B, Siegel E, et al. Results of autologous stem cell transplant in multiple myeloma patients with renal failure. *Br J Haematol*. 2001;114(4):822-829.
60. Dimopoulos MA, Sonneveld P, Leung N, et al. International myeloma working group recommendations for the diagnosis and management of myeloma-related renal impairment. *J Clin Oncol*. 2016;34(13):1544-1557.
61. Bender RA, Castle MC, Margileth DA, Oliverio VT. The pharmacokinetics of [3H]-vincristine in man. *Clin Pharmacol Ther*. 1977;22(4):430-435.
62. Yoshida H, Goto M, Honda A, et al. Pharmacokinetics of doxorubicin and its active metabolite in patients with normal renal function and in patients on hemodialysis. *Cancer Chemother Pharmacol*. 1994;33(6):450-454.
63. Bagley CM Jr, Bostick FW, DeVita VT Jr. Clinical pharmacology of cyclophosphamide. *Cancer Res*. 1973;33(2):226-233.
64. de Jonge ME, Huitema AD, Rodenhuis S, Beijnen JH. Clinical pharmacokinetics of cyclophosphamide. *Clin Pharmacokinet*. 2005;44(11):1135-1164.
65. Scheers E, Leclercq L, de Jong J, et al. Absorption, metabolism, and excretion of oral 14C radiolabeled ibrutinib: an open-label, phase I, single-dose study in healthy men. *Drug Metab Dispos*. 2015;43(2):289-297.
66. Boey O, Van Hooland S, Woestenburg A, Van der Niepen P, Verbeelen D. Methotrexate should not be used for patients with end-stage kidney disease. *Acta Clin Belg*. 2006;61(4):166-169.
67. Cheung KK, Chow KM, Szeto CC, Tai MH, Kwan BC, Li PK. Fatal pancytopenia in a hemodialysis patient after treatment with low-dose methotrexate. *J Clin Rheumatol*. 2009;15(4):177-180.
68. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol*. 1989;7(11):1748-1756.
69. Watanabe R, Takiguchi Y, Moriya T, et al. Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. *Br J Cancer*. 2003;88(1):25-30.
70. Kurisu A, Hata T, Owada A. Full-dose chemotherapy for esophageal cancer patient under hemodialysis. *Nephron*. 2002;92(4):960.
71. Gori S, Lunardi G, Inno A, et al. Pharmacokinetics of oxaliplatin in a hemodialyzed patient: chemotherapy dose adjustment and timing of dialysis. *Clin Colorectal Cancer*. 2014;13(4):260-263.
72. Abbruzzese JL, Grunewald R, Weeks EA, et al. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. *J Clin Oncol*. 1991;9(3):491-498.
73. Hande KR, Wedlund PJ, Noone RM, Wilkinson GR, Greco FA, Wolff SN. Pharmacokinetics of high-dose etoposide (VP-16-213) administered to cancer patients. *Cancer Res*. 1984;44(1):379-382.
74. Holthuis JJ, Van de Vyver FL, van Oort WJ, Verleun H, Bakaert AB, De Broe ME. Pharmacokinetic evaluation of increasing dosages of etoposide in a chronic hemodialysis patient. *Cancer Treat Rep*. 1985;69(11):1279-1282.
75. English MW, Lowis SP, Peng B, et al. Pharmacokinetically guided dosing of carboplatin and etoposide during peritoneal dialysis and haemodialysis. *Br J Cancer*. 1996;73(6):776-780.
76. Zhao B, Chen R, O'Connor OA, et al. Brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive haematologic malignancies and hepatic or renal impairment. *Br J Clin Pharmacol*. 2016;82(3):696-705.
77. Horwitz ME, Spasojevic I, Morris A, et al. Fludarabine-based nonmyeloablative stem cell transplantation for sickle cell disease with and without renal failure: clinical outcome and pharmacokinetics. *Biol Blood Marrow Transplant*. 2007;13(12):1422-1426.
78. Lichtman SM, Etcubanas E, Budman DR, et al. The pharmacokinetics and pharmacodynamics of fludarabine phosphate in patients with renal impairment: a prospective dose adjustment study. *Cancer Invest*. 2002;20(7–8):904-913.

How to cite this article: Yasuda H, Yasuda M, Komatsu N. Chemotherapy for non-Hodgkin lymphoma in the hemodialysis patient: A comprehensive review. *Cancer Sci*. 2021;112:2607–2624. https://doi.org/10.1111/cas.14933