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

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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 ⁹⁰⁹-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; DCR, 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.

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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), Table 2 (various other regimens), and Table 3 (stem cell transplantation), and are discussed below. Recommendations on individual drug administrations are summarized in Table 4. 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. 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/m², day 1 CPA 750 mg/m², and days 1-5 PSL 40 mg/m² (100 mg/body in some cases). A standard CHOP regimen consists of day 1 VCR 1.4 mg/m², day 1 DXR 50 mg/m², day 1 CPA 750 mg/m², 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. 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. Some investigators have recommended a 10%-20% dose reduction of DXR and VCR in HD patients, while most others have recommended the standard dose. Data concerning removal of DXR and VCR by HD are limited, and therefore these drugs should be administered after HD. 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. Approximately 30%-60% of CPA is eliminated by the kidneys as the parent drug or its metabolites, and a dose reduction of 25% has been recommended in HD patients. CPA is removed by dialysis and therefore should be administered after HD sessions. 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).

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. 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. 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. 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. 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.
| 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<sup>10</sup> | M   | 54  | B-cell NHL       | R         | 375 mg/m<sup>2</sup>              | 8                                    | Hyperkalemia (grade 4)                                                                | CR       | Alive                      |
| 2           | Morita et al, 2010<sup>11</sup> | M   | 76  | B-cell NHL       | R         | 375 mg/m<sup>2</sup>              | 6                                    | N/A                                                                                  | CR       | Died of PD 14 months after diagnosis |
| 3           | Ablin et al, 1972<sup>12</sup> | 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<sup>13</sup> | M   | 27  | NHL              | CPA       | 600 mg/body                         | 1                                    | N/A                                                                                  | N/A      | N/A                        |
| 5           | Gianviti et al, 1989<sup>14</sup> | M   | 9   | BL               | VCR + CPA | N/A                                | N/A                                  | Abdominal hemorrhage, tumor reduction                                             | Died of abdominal hemorrhage |
| 6           | Ozaltin et al, 2004<sup>15</sup> | M   | 17  | B-cell NHL       | VCR + CPA + PSL | VCR: 1 mg/m<sup>2</sup> day 1 CPA: 200 mg/m<sup>2</sup> days 1-5 PSL: 60 mg/m<sup>2</sup> days 1-7 | 1                                    | N/A                                                                                  | PR       | Alive                      |
| 7           | Christopoulos et al, 2009<sup>16</sup> | F   | 65  | T-LGLL           | CVP       | standard                            | 1                                    | Severe sepsis, pulmonary infection                                               | no response | Died of sepsis 6 months later   |
| 8           | Cavoli et al, 2012<sup>17</sup> | M   | 72  | MZL              | CVP       | N/A                                | N/A                                  | N/A                                                                                  | N/A      | N/A                        |
| 9           | Miyata et al, 2017<sup>18</sup> | M   | 77  | MCL              | CVP       | CPA: 325 mg/m<sup>2</sup> VCR: 1.4 mg/m<sup>2</sup> 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<sup>6</sup> | F   | 47  | DLBCL            | VCR + CPA + DEX | VCR 1.8 mg/body CPA 1000 mg/body DEX 40 mg/body<sup>a</sup> | N/A                                  | TLS Hyperkalemia (grade 3)                                                      | N/A      | N/A                        |
| 11          | Yasuda et al, 2021<sup>19</sup> | M   | 73  | MCL              | CVP       | CPA: 375 mg/m<sup>2</sup> VCR: 1.4 mg/m<sup>2</sup> PSL: 100 mg/body days 1-5 | 1                                    | Thrombocytopenia (grade 3)                                                        | tumor reduction | proceeded to ibrutinib therapy |
| 12          | Weng et al, 2010<sup>20</sup> | 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)
| 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, 2016³ | 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, 2016³ | M   | 82  | FL             | R-CVP            | RDI 54%                             | 6                                     | Neutropenia (grade 3)                                                             | CR       | alive at 34 months from diagnosis |
| 15          | Gangireddy et al, 2019⁹¹ | M   | 80  | DLBCL          | R-miniCHOP       | N/A                                 | N/A                                   | Severe pancytopenia, MOF                                                          | N/A      | died                        |
| 16          | Paganelli et al, 1989²² | 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, 2000⁹⁹ | M   | 73  | BL             | CHOP             | N/A                                 | 1                                     | Pulmonary infection, sepsis                                                       | N/A      | died on day 3 of CHOP           |
| 18          | Peddi et al, 2015²⁴ | M   | 54  | MCL            | CHOP             | N/A                                 | N/A                                   | N/A                                                                              | N/A      | N/A                         |
| 19          | Hamadah et al, 2017²⁵ | 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, 2017²⁵ | N/A | N/A | DLBCL          | CHOP             | 20% reduction of CPA                 | 1                                     | FN, infection                                                                   | PR       | 79-month follow up             |
| 21          | Hamadah et al, 2017²⁵ | N/A | N/A | T-cell NHL     | CHOP-E            | Standard                             | 1                                     | FN, infection, cardiac complication                                               | PD       | 1-month follow up             |
| 22          | Hamadah et al, 2017²⁵ | N/A | N/A | T-cell NHL     | CHOP-E            | 25% reduction of CPA                 | 1                                     | TLS, FN                                                                         | N/A      | 5-month follow up             |
| 23          | de Barros Pontes et al, 2013²⁶ | 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, 2007²⁷ | 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, 2008²¹ | M   | 47  | DLBCL          | R-CHOP + radiotherapy | N/A                                 | 1                                     | N/A                                                                              | improvement | alive in CR at 20 months after diagnosis |
| 26          | Jorge et al, 2010²¹ | F   | 51  | DLBCL          | R-CHOP            | standard                             | N/A                                   | N/A                                                                              | N/A      | alive                       |
| 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<sup>19</sup> | M   | 64  | DLBCL   | R-CHOP    | 50% reduction of DXR and CPA; PSL administered at 60 mg/m<sup>2</sup> 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<sup>3</sup>    | 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<sup>3</sup>    | 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<sup>3</sup>    | 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<sup>3</sup>    | 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<sup>3</sup>    | 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<sup>25</sup> | N/A | N/A | DLBCL   | R-CHOP    | 25% reduction of CPA                  | 1                              | FN, infection | CR       | 55-month follow up |
| 34          | Hamadah et al, 2017<sup>25</sup> | 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<sup>25</sup> | N/A | N/A | DLBCL   | R-CHOP    | 25% reduction of CPA                  | 3                              | Mucositis | CR       | 38-month follow up |
| 36          | Hamadah et al, 2017<sup>25</sup> | N/A | N/A | DLBCL   | R-CHOP    | 25% reduction of CPA                  | 6                              | Cardiac complication | CR       | 10-month follow up |
| 37          | Heggermont et al, 2017<sup>20</sup> | M   | 51  | DLBCL   | R-CHOP    | N/A                                   | N/A                            | N/A | improvement | CR after 3 courses of R-CHOP |
| 38          | Leite et al, 2017<sup>31</sup>  | M   | 20  | DLBCL   | R-CHOP    | N/A                                   | N/A                            | N/A | improvement | alive |
| 39          | Palamuthusingam et al, 2017<sup>32</sup> | M   | 65  | MCL     | R-CHOP    | Standard                              | 5                              | N/A | CR        | alive in CR at 12 months |

(Continues)
| 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 | 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 | M   | 55  | DLBCL   | R-CHOP | N/A | 6 | N/A | PD | proceeded to salvage chemotherapy due to PD |
| 42         | Fukuno et al, 2013 | M   | 60  | FL      | R-THP-COP | N/A | 4 | N/A | PR | relapsed and proceeded to salvage therapy |
| 42         | Fukuno et al, 2013 | 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 90Y-ibritumomab tiuxetan therapy |
| 43         | Ochi et al, 2016 | 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: 90Y, 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.

aDexamethasone 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 | 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 | 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 | 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 | 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 | F   | 70  | SMZL    | R + Chlorambucil | R: 375 mg/m² day 1 Chlorambucil: 6 mg/m² (day 1-10) | 6                                     | Mild fever and chills | CR       | Alive in CR at 8 months after treatment initiation |
| 48          | Aw et al., 2018 | 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 | 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 | N/A | 61  | FL      | BR       | N/A                                   | 6                                     | N/A           | PR       | DLBCL transformation at 17 months |
| 51          | Kudo et al., 2017 | M   | 58  | LPL     | BR       | R: 375 mg/m² day 1 Bendamustine: 90 mg/m² day 2,3 | 6                                     | Severe pneumonia | N/A     | Died of pneumonia after course 6 |
| 52          | Ettleson et al., 2019 | M   | 72  | MCL     | Bendamustine + Ara-C | Bendamustine 90 mg/m² day 1.2 Ara-C 500 mg/m² day 1-3 | 1                                     | N/A           | Improvement | Alive |
| 53          | Murashima et al., 2009 | M   | 58  | PCNSL   | R + MTX + temozolomide | Course 1: MTX 3 g/m²; Course 2: MTX 6 g/m²; Course 3: MTX 4 g/m²; R: N/A, temozolomide: N/A | 4                                     | Catheter infection | N/A     | N/A |

(Continues)
| 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 | F   | 52  | PCNSL   | R + MTX + DEX + IT Ara-C | R: 375 mg/m² MTX: 1 g/m² 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   | M   | 55  | DLBCL   | R-GDC     | R: 375 mg/m² day 3 gemcitabine: 1000 mg/m² 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   | N/A | 61  | DLBCL transformation | R-GemOx | R: N/A Gemcitabine: 1000 mg/m² day 1 Oxaliplatin: 50 mg/m² day 1 | 3                | N/A                              | PR         | N/A |
| 55          | Pöschl et al., 1993   | M   | 8   | BL      | PSL + CPA + MTX + DXR + Ara-C | PSL: 30 mg/body day 1-14 CPA: 145 mg/m² day 1-12 CPA: 230 mg/m² day 1-15 MTX: 25 mg/m² day 1-42 MTX: 16 mg/m² day 1-42 DXR: 2 mg/m² day 18, 19, 21, 23, 24, 46, 47, 53, 54, 96, 97 Ara-C: 100 mg/m² for 7 days on week 4 | 1                | Fever                            | PD         | Died of PD 5 months after treatment initiation |

(Continues)
| 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 | F   | 48  | MCL      | Ara-C                                           | 1 g/m² (capped at 2 g/body) day 1,2                                                                   | 3                                       | No neurotoxicity and no other unexpected toxicities                              | PR       | Alive                    |
| 41          | Morita et al., 2020 | M   | 55  | DLBCL    | CHASER                                          | R: 375 mg/m² day 1 CPA: 600 mg/m² day 2 ETP: 50 mg/m² day 2-4 Ara-C: 1000 mg/m² day 4,5 DEX: 33 mg/body day 2,4,5 | 2                                       | N/A                                                                              | PR       | Proceeded to ASCT             |
| 57          | Hamadah et al., 2017 | 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 | F   | 71  | NHL      | Mitoxantrone + CPA + VCR + hydrocortisone       | Mitoxantrone: 10 mg/m² CPA: 650 mg/m² 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 | F   | 72  | B-cell NHL | Mitoxantrone + prednimustine                   | Mitoxantrone: 8 mg/m² day 1 for course 1-3, 8 mg/m² day 1,2 for course 4 Prednimustine: 100 mg/m² 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 | 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 | 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)
| 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 | 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 | 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 | M   | 44  | 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.
| 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 | 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 | M   | 69  | MCL     | FLU + MEL (ASCT conditioning) | FLU: 6 mg/m² day 1-4 MEL: 100 mg/m² day 5 | 1 | FN, mucositis | CR | Alive in CR at 16 months post-ASCT |
| 41          | Morita et al, 2020 | M   | 55  | DLBCL   | MEL + BU (ASCT conditioning) | MEL: 100 mg/m² 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 | 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.
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, therefore the pharmacokinetics of chlorambucil are considered to be basically not influenced by renal deficiency. 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. 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, therefore the pharmacokinetics of irbutinib are 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.

4.4 Bendamustine

Bendamustine is a purine analog/alkylator hybrid drug that is primarily metabolized in the liver, with limited renal elimination. 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. Another study of 12 multiple myeloma patients with severe renal impairment, including five HD patients undergoing two consecutive days of bendamustine 120 mg/m² at 4-week intervals, demonstrated that higher frequencies of leukocytopenia and thrombocytopenia were observed in patients with normal kidney function. 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/m² 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 administering 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/m² 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/m² 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.4,5,6,8 Cisplatin has been administered to HD patients with lung cancer at doses ranging from 40 to 80 mg/m², 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/m² 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/m².71 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/m², 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.50 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.5

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). 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/m² (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. 

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. 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. 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. Gemcitabine has been administered at 1000 mg/m² in two NHL patients on HD (cases 41 and 50), in which information on adverse events was not commented on.

4.9 | Etoposide

Etoposide is a topoisomerase-II inhibitor of which approximately 40% is excreted by the kidneys. Some studies have reported that pharmacokinetic parameters of etoposide were similar between HD patients and patients with normal renal function, whereas others have demonstrated an AUC rise and prolonged half-life in patients with renal insufficiency, including patients on HD. Etoposide dose reductions of 50%, translating to actual dosing of 25-75 mg/m², have been proposed by investigators for patients on HD. Etoposide is not removed by HD and administration can be done before or after HD sessions. Three NHL patients on HD have been treated with etoposide (cases 21, 22, and 57), when in conjunction with CHOP, and one as part of a modified proMACE/CytaBOM regimen (prednisolone + methotrexate + doxorubicin + cyclophosphamide + etoposide/cytarabine + bleomycin + vincristine + methotrexate). 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 phosphoramido mustard, but also gives birth to the urotoxic metabolite acrolein, and the nephrotoxic and neurotoxic metabolite chloroacetaldehyde. 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/m² of ifosfamide which was administered on a single day or divided between two separate days, and they concluded that ifosfamide treatment was feasible. However, other investigators contraindicate or look upon its use as controversial in HD patients, and definite recommendations cannot be made.

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

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

90Y-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. 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. 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.

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, 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/m² 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.

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