Polivy in Patients with Renal Impairment with or without Dialysis

This article responds to your request for information on the use of Polivy® (polatuzumab vedotin) in patients requiring dialysis. This response was developed according to the principles of evidence-based medicine and contains data from clinical literature.

In brief

Considerations for the use of Polivy in patients with renal impairment

- Dedicated clinical studies of excretion of Polivy have not been conducted. Polivy is expected to undergo proteolytic catabolism in patients.
- Polivy clinical studies enrolled patients with CrCL ≥40 mL/min unless due to the underlying disease of lymphoma.
- In population PK analysis, patients with mild or moderate renal impairment (CrCL of 30-90 mL/min) had PK exposures similar to that of normal patients (CrCL >90 mL/min). Severe renal impairment with or without dialysis were limited in number and hence, the effect on the PK of Polivy in these patients is unknown.
- In a pooled safety analysis
    - Polivy-related AEs leading to treatment discontinuation seem to increase with renal impairment, so careful monitoring is recommended in patients with moderate renal insufficiency, and
    - very limited data exist for patients with severe and end-stage renal insufficiency; therefore, no conclusions can be drafted.
- No Polivy dose adjustments is required in patients with mild to moderate renal impairment. A recommended dose has not been determined for patients with CrCL <30mL/min due to limited data.
- Currently there are no published case reports on the use of Polivy in patients with severe renal impairment.

Considerations for the use of Polivy in patients requiring dialysis

- The PK, safety, and efficacy of Polivy in patients on dialysis have not been formally established. The use of Polivy is not contraindicated in patients requiring dialysis.
- Polivy has a large molecular weight (145 kDa) and is expected to continue to circulate in serum during and after dialysis.
- Yasuda et.al. conducted PK studies of Polivy when administered at 1.2 mg/kg to a DLBCL patient on HD, and compared the results with that of non-HD patients. The authors concluded that Polivy therapy may be a relatively safe treatment method for DLBCL patients on HD.

Abbreviations

ADC=antibody drug conjugate

AEs=adverse events

CrCL=creatinine clearance

ESRD=end-stage renal disease

G-CHP=obinutuzumab, cyclophosphamide, doxorubicin, and prednisone

HD=haemodialysis

kDA=kilodaltons

MMAE-ADC=mono-methyl auristatin E-antibody drug conjugate

NHL=non Hodgkin's lymphoma

PK=pharmacokinetics

R-CHP=rituximab, cyclophosphamide, doxorubicin, and prednisone

SAEs=serious adverse event

Metabolism of Polivy

Dedicated clinical studies of excretion of Polivy have not been conducted. However, Polivy is expected to undergo proteolytic catabolism in patients based on

- preclinical studies of Polivy in rats[1]
- clinical data of brentuximab vedotin, an MMAE-ADC with the identical linker and cytotoxic agent as Polivy in lymphoma patients,[1] and
- metabolism and elimination pathways of ADCs as suggested in the literature.[2]

Considerations for the use of Polivy in patients with renal impairment

PK of Polivy in patients with renal impairment

The potential impact of renal function on the PK of Polivy was assessed by a population PK approach.[1]

Patients from Polivy Phase 1, 2, and 3 clinical trials were included in the population PK analysis. The eligibility criteria in Polivy clinical studies was to enroll patients with CrCL ≥40 mL/min unless due to the underlying disease of lymphoma.[1,3] Only four patients with severe renal impairment (CrCL 15-29 mL/min), and no patients with ESRD with or without dialysis were included in the population PK analysis.[1,3,4] Due to the limited data, the effect of severe renal impairment and ESRD with or without dialysis on the PK of Polivy is therefore unknown. Patients with mild or moderate renal impairment (CrCL of 30-90 mL/min) had PK exposures similar to that of normal patients (CrCL >90 mL/min).

Safety analysis of the use of Polivy in patients with renal impairment

The pooled population for safety analysis (N=501) comprised of all patients from the POLARIX and GO29044 clinical studies with previously untreated DLBCL receiving Polivy 1.8 mg/kg in combination with R-CHP or G-CHP.[5]

In this pooled population, in both treatment arms, with the severity of renal impairment, there was an increase in the proportion of patients who experienced

- all-grade AEs
- grade ≥ 3 AEs
- SAEs, and

- AEs leading to any study treatment discontinuation.[5]

There was very limited data on severe renal impairment (N=2).[5]

Recommendation for Polivy dose adjustment in patients with renal impairment

No Polivy dose adjustments are required in patients with mild to moderate renal impairment.[1,4] A recommended dose has not been determined for patients with CrCL <30mL/min due to limited data.[1,4] See the locally approved prescribing information for further information on the PK of Polivy.

Published reports on the use of Polivy in patients with severe renal impairment

There are no published case reports on the use of Polivy in patients with severe renal impairment.

Considerations for the use of Polivy in patients requiring dialysis

PK of Polivy in patients on dialysis

The PK, safety and efficacy of Polivy in patients on dialysis has not been formally assessed.[4]

Permeability of dialysis membranes

Dialysis membranes are typically permeable to molecules up to 15 kDa.[6] Larger molecules are retained by dialysis membranes.

As Polivy has a molecular weight of approximately 145 kDa,[7] it should not be filtered out of the body during dialysis. Polivy is therefore expected to continue to circulate in serum after dialysis.

Published reports on the use of Polivy in patients requiring dialysis

Yasuda et.al. conducted PK studies of Polivy when administered at a reduced dose of 1.2 mg/kg to a DLBCL patient on HD, and compared the results with that of non-HD patients.[8] The study showed that

- serum concentration levels of MMAE-ADC before and after HD sessions did not significantly differ, meaning that dialysability of Polivy is minimal, likely due to its high molecular weight
- although a small molecule, serum levels of unconjugated MMAE also did not significantly differ before and after HD sessions. This is because the elimination of both conjugated and unconjugated MMAE through HD was likely limited due to its relatively high protein-binding rates and a large volume of distribution, and
- serum concentration–time curves of both conjugated and unconjugated MMAE in the HD patient were similar compared to that of non-HD patients.

The authors concluded that Polivy therapy may be a relatively safe treatment method for DLBCL patients on HD.[8]

Consideration for use of Polivy in patients requiring dialysis

The use of Polivy in patients requiring dialysis is not contraindicated, however the safety and efficacy has not been formally assessed.[4] Administering Polivy to patients on dialysis would be a decision made by the treating physician, and should be based upon an appropriate risk-benefit assessment.

References

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8. Yasuda H, Kaga N, Taka H, et al. Polatuzumab vedotin pharmacokinetics in a hemodialysis patient with diffuse large B-cell lymphoma. Cancer Chemother Pharmacol 2023;https://www.ncbi.nlm.nih.gov/pubmed/37750932