


Glucarpidase for Treating Adults with Delayed Methotrexate Elimination Due to Impaired Renal Function: An Economic Simulation Analysis

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Background: Glucarpidase is indicated for treating delayed methotrexate (MTX) elimination due to impaired renal function. Although glucarpidase is capable of rapidly eliminating MTX independent of renal clearance, its cost can be perceived as a barrier to use. However, no published economic analyses have evaluated glucarpidase relative to comparable treatments.

Purpose: To assess the economic value of glucarpidase for treating adult patients in the United States (US) who experience delayed MTX elimination due to impaired renal function.

Methods: A decision tree model was developed to assess the economic value of glucarpidase. The short-term inpatient management of patients as well as long-term survival were simulated. Costs associated with the use of glucarpidase were compared against other methods for treating delayed MTX elimination due to impaired renal function under two scenarios: current practice (ie, mix of timely/delayed use of glucarpidase, hemodialysis, or supportive care [SC] alone) as compared with proposed practice (ie, timely glucarpidase administration within 60 hours for all eligible patients). Hypothetical practical scenarios for US institutions were also considered.

Results: For adult patients with delayed MTX elimination, proposed practice as compared to current practice was associated with an increased cost of \$20,024 per patient, not considering any incremental reimbursement associated with glucarpidase administration. Importantly, early treatment with glucarpidase, within 60 hours, was shown to be less expensive per patient than delayed glucarpidase treatment or treating with hemodialysis, but more expensive than SC alone. However, proposed practice was associated with multiple clinical benefits, including shorter hospital length of stay. For hypothetical practical scenarios, minimal shifts in treatment patterns had minimal cost impacts.

Conclusion: Treatment of all eligible patients with glucarpidase within 60 hours was associated with an increased cost per patient (relative to current practice) but substantial improvements in clinical outcomes. Timely glucarpidase use was less expensive than delayed glucarpidase or hemodialysis.

Keywords: chemotherapy, toxicity, costs, outcomes

Introduction

Methotrexate (MTX) is an antifolate widely used to treat cancers (eg, lymphomas, acute lymphoblastic leukemia, osteosarcoma) and autoimmune diseases.¹ As a cancer therapy, MTX may be given at doses exceeding 500 mg/m² (high-dose MTX; HDMTX).¹ It is primarily eliminated by the kidney through passive glomerular filtration and active tubular reabsorption and secretion; as such, renal function is a major determinant of MTX clearance.² In a minority of patients, estimated at less than 15%, administration of HDMTX is followed by delayed MTX elimination due to impaired renal function.^{3–7} The resulting elevated MTX plasma concentration and tissue accumulation can lead to a range of severe

toxicities (eg, hepatotoxicity, mucositis, myelosuppression, and nephrotoxicity) and appreciable morbidity and mortality, in part because of cancer treatment disruption.^{1,8}

To reduce the risk of toxicity from delayed MTX elimination due to impaired renal function, HDMTX treatment is typically accompanied by supportive care (SC) measures including fluid hydration, urine alkalinization, and leucovorin (and, in many cases, high-dose leucovorin [HDLV]).^{1,8} Patients are monitored regularly for signs of delayed MTX elimination, since early intervention is of crucial importance to not only lower the likelihood of toxicity but also minimize the impact to cancer treatment.¹ In the event of delayed MTX elimination due to impaired renal function, treatment options include HDLV, hemodialysis, and/or glucarpidase.⁸ Leucovorin has to compete with MTX to be taken up by cells and thus is less effective when MTX concentrations are too high ($>10 \mu\text{M}$).⁸ Whereas leucovorin requires the restoration of normal renal function for MTX elimination to proceed, high-flux hemodialysis can improve MTX clearance. However, hemodialysis typically requires multiple sessions, extends inpatient stay, may lead to severe complications, and can be followed by a rebound in MTX levels.^{1,9}

Glucarpidase (Voraxaze[®], BTG International Inc.) is a recombinant carboxypeptidase that rapidly reduces plasma MTX concentration by hydrolyzing MTX into two inactive metabolites.⁸ Administered intravenously, glucarpidase can substantially lower the plasma MTX concentration by 97% within 15 minutes, independent of renal clearance, with 91% of patients sustaining MTX reduction for up to 8 days.¹⁰ Adverse events (AEs) are minimal with glucarpidase, with the most common reactions generally being grade 1 or 2.¹¹ In 2012, the United States (US) Food and Drug Administration (FDA) approved glucarpidase for lowering toxic plasma MTX levels ($>1 \mu\text{mol/L}$) in adult and pediatric patients with delayed MTX clearance (plasma MTX concentrations greater than 2 standard deviations of the mean MTX excretion curve specific for the dose of MTX administered) due to impaired renal function.¹¹ Notably, the FDA label for MTX explicitly recommends glucarpidase use for this patient population.¹²

A consensus guideline identified optimal glucarpidase administration as that occurring within 48–60 hours from the start of HDMTX infusion (hereafter referred to as “timely glucarpidase”).⁸ Although glucarpidase can still effectively reduce plasma MTX concentrations if given beyond 60 hours (“delayed glucarpidase”), delayed glucarpidase administration may impact the prevention of life-threatening toxicities, as MTX toxicity is both concentration and time dependent.⁸ A study of 76 patients treated with leucovorin and glucarpidase demonstrated that treatment with glucarpidase within 96 hours of HDMTX administration without pre-existing grade 4 adverse events resulted in only 14% experiencing grade 4 toxicity compared to 55% of patients treated with glucarpidase after 96 hours.¹³ Similarly, in a study of 476 patients, timely administration of glucarpidase reduced mortality rates from 22% to 10.9%.¹⁴

Although there are no head-to-head randomized controlled trials comparing glucarpidase with other interventions (reflecting its infrequent use, heterogeneous target population, and ethical considerations), several key observational studies have demonstrated superior glucarpidase efficacy. A pooled analysis of four multicenter single-arm compassionate-use clinical trials demonstrated that (1) glucarpidase rapidly and consistently reduced plasma MTX concentrations in patients with HDMTX-induced renal toxicity and (2) 64% of patients with Common Terminology Criteria for AEs grade 2 or higher renal impairment recovered to grade 0 or 1 after a median of 12.5 days following glucarpidase administration.¹⁰ A retrospective study using Medicare claims data (2010–2017) found that older adult cancer patients treated with glucarpidase had lower inpatient mortality and 90-day mortality compared with non-glucarpidase patients (including a subset of patients who received hemodialysis), and patients who received glucarpidase also had both shorter overall hospital length of stay (LOS) and shorter intensive care unit (ICU) LOS.¹⁵ Based on a systematic literature review and modified Delphi panel, the EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup recommended against hemodialysis instead of administering glucarpidase for patients with severe MTX toxicity receiving standard care.¹⁶ The clinical value associated with the administration of glucarpidase for patients with delayed MTX clearance is well accepted, and its use is widely recommended.^{5,8,12,16,17}

Although the clinical value of glucarpidase in patients with delayed MTX elimination due to impaired renal function is well accepted, this medication may be underutilized in practice. A recent consensus guideline for the stocking of antidotes in emergency departments recommended that hospitals should stock glucarpidase,¹⁸ but this is not routinely done by many institutions.⁹ There may be hesitancy, or funding restrictions, around acquiring and prescribing glucarpidase due to its cost.^{9,19} However, there have been no published economic analyses to evaluate the cost-effectiveness or

budget impact of glucarpidase. There are other costs (eg, hospitalization, SC, hemodialysis, monitoring) associated with delayed MTX elimination treatment that are important to consider when evaluating the impact of glucarpidase use.

The objective of this study was to conduct an economic analysis for the use of glucarpidase in adults in the US who experience delayed MTX elimination due to impaired renal function after HDMTX, to (1) compare outcomes associated with current practice versus proposed practice (ie, timely access to glucarpidase within 60 hours for all patients who are eligible) and (2) determine the clinical and cost impact of timely glucarpidase use versus delayed glucarpidase use, hemodialysis, or SC alone.

Methods

Model Overview

Economic modelling seeks to estimate costs and clinical outcomes as accurately as possible, informing the simulation with simplifying assumptions to reflect complex disease and treatment paradigms. A decision tree model was developed in Microsoft Excel (Microsoft 365) from the US hospital institution perspective to simulate clinical outcomes and costs associated with the treatment of adult patients with delayed MTX elimination due to impaired renal function, as defined in the FDA label for glucarpidase,¹¹ who received one of four treatments: SC alone or in conjunction with timely glucarpidase, delayed glucarpidase, or hemodialysis. The model compared two hypothetical scenarios: current practice (ie, fewer patients on glucarpidase than indicated based on the FDA label, with delayed or no administration in many patients) versus proposed practice (ie, timely glucarpidase administration for all eligible patients). The analysis was selected to evaluate the most extreme cost impact associated with shifting practice patterns, that is, if all eligible patients were to receive glucarpidase. The core model considered inpatient care and used a two-month time horizon; a short time horizon prevented the need for extrapolation of clinical outcomes over the long-term. A longer (3-year) time horizon was considered to estimate cancer survival associated with ability to resume chemotherapy after treatment for delayed MTX elimination.

Model Design

The model structure is illustrated in [Figure 1](#). Adult patients (18 years of age or older) who received HDMTX and experienced delayed MTX elimination due to impaired renal function in the simulation received one of four treatments (SC alone, or SC in conjunction with timely glucarpidase, delayed glucarpidase, or hemodialysis). Patients receiving SC alone may have also received HDLV. Patients were modelled to have experienced one of three outcomes: (1) recovery and rechallenge with HDMTX, (2) recovery but no rechallenge with HDMTX, or (3) death. Patients who received HDMTX but did not experience delayed MTX elimination due to impaired renal function were not considered.

Clinical outcomes and costs were modeled to calculate the difference between current practice patterns and proposed practice. Only costs incurred during inpatient stay were considered. Costs for cancer treatment (eg, chemotherapy) were not considered because it was assumed that those would not differ by treatment arm. Costs associated with readmissions related to delayed MTX elimination (eg, acute kidney injury, mucositis) were also not considered, which was expected to underestimate the benefit associated with glucarpidase use as timely glucarpidase would likely reduce long-term damage associated with slow recovery from high MTX levels.

Incremental total costs (ie, the difference in all healthcare costs when shifting from current practice to proposed practice) and estimated inpatient survival for current practice versus proposed practice were used to calculate the cost per additional inpatient survival under the proposed practice scenario.

Model Parameters

Model inputs and their sources are shown in [Table 1](#). A series of targeted literature searches were used to identify model inputs. The starting patient population was chosen to reflect an average number of patients treated with HDMTX at a large US institution in one year. It was estimated that 6.4% of adult patients treated with HDMTX may experience delayed MTX elimination due to impaired renal function, using the proportion of patients experiencing acute renal failure after treatment with HDMTX as a proxy to inform this.³ Market research data were used to inform the mix of treatments used in current

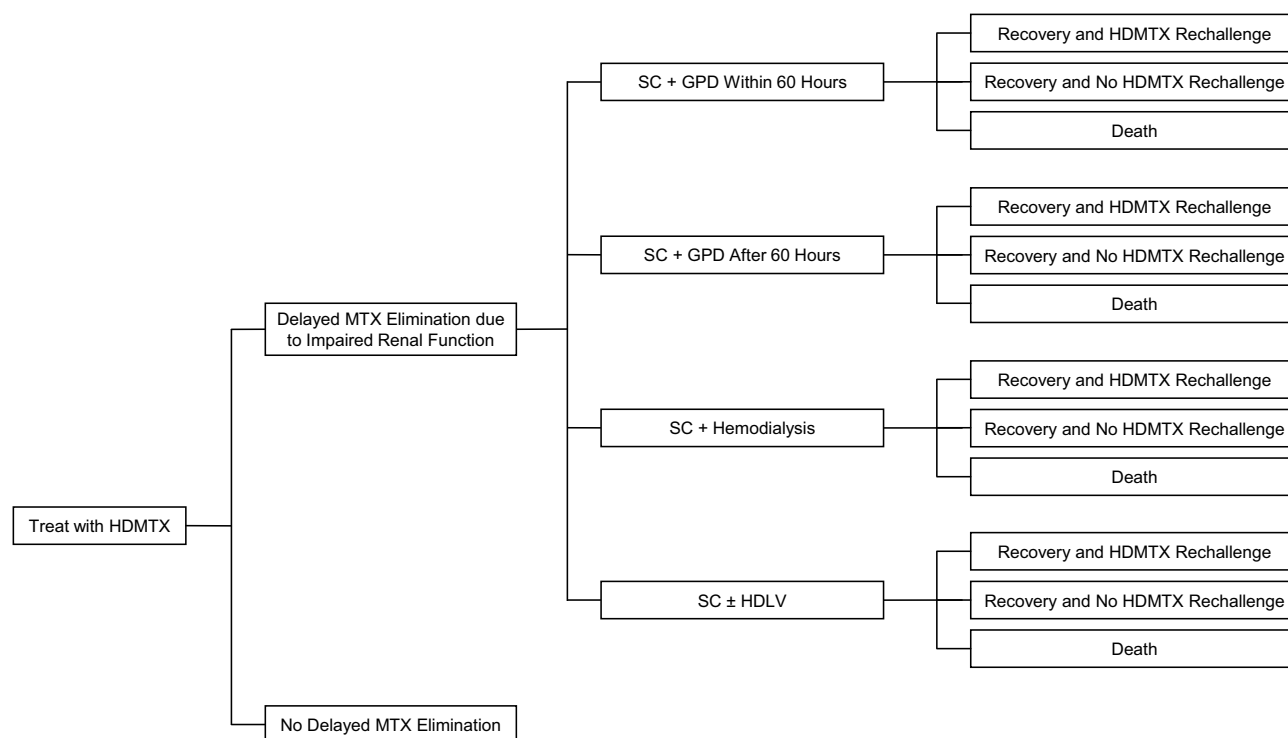


Figure 1 Decision tree model flowthrough diagram. The timing of GPD (within or after 60 hours) is from the start of HDMTX infusion.

Abbreviations: GPD, glucarpidase; HDLV, high-dose leucovorin; HDMTX, high-dose methotrexate; MTX, methotrexate; SC, supportive care.

practice, which estimated that 10.8% of patients receive timely glucarpidase, 7.2% received delayed glucarpidase, 30% received dialysis, and the rest received supportive care, and it was assumed in the proposed practice scenario that 100% of eligible patients receive glucarpidase in a timely manner. To enable the evaluation of whole patients in the analysis (ie, one patient receiving glucarpidase in the current scenario), and optimize interpretability of the results, a starting population of 78 patients was assumed. Drug costs, SC costs, and monitoring costs used in the model were current at the time of analysis (June 2022). Where possible, a single reference was used to inform a given input across treatment arms, to reduce the bias associated with comparing divergent study designs. For example, many clinical inputs, including length of stay and inpatient mortality, were derived from a retrospective analysis of patients with delayed clearance of MTX who were treated with glucarpidase. This dataset was a 2010–2017 Medicare claims retrospective study that captured real-world evidence on the clinical experience of patients with MTX toxicity, reflecting the variability in patient experience (eg, different cancer types, different MTX dosing regimens, different supportive care procedures) that is inherent in clinical practice.¹⁵ In this study, there was a small number of patients (13%) who received glucarpidase as well as dialysis, so the cost of dialysis for those patients was included in the present model so as to not bias in favor of glucarpidase. It was assumed that adult patients only require one round of glucarpidase treatment. Further, it was assumed that adult patients receive 4 vials of glucarpidase, based on the recommended weight-based dose in the FDA label and the average adult weight in the US,¹¹ and to align with efficacy estimates available for glucarpidase. Additional assumptions for individual model inputs are described in Table 1.

Reimbursement was not considered in the model, due to the large variability in reimbursement rates across patients and facilities. It is expected that glucarpidase use is associated with incremental reimbursement rates, and therefore the economic impact to the institution associated with glucarpidase is expected to be less in real world practice than reported in the model.

Sensitivity Analyses

A sensitivity analysis using model inputs for pediatric patients (where available) was conducted to understand any differences in model results compared with adults. Pediatric patients were not included in the base case analysis because key model inputs (eg, inpatient mortality rates, average LOS) specific to this age group were not available.

Table I Model Inputs for the Base Case Analysis

Parameter	Value	Source	Notes
Epidemiology			
Number of adult patients treated with HDMTX	78	Assumption	Assumption to ensure a round number of patients were assigned treatments, to improve the interpretability of results
Proportion with delayed MTX elimination due to impaired renal function	6.4%	de Miguel et al (2008) ³	Source reported proportion of adult patients treated with HDMTX who experienced acute renal failure (assumed to be equivalent to AKI, a proxy for delayed MTX elimination due to impaired renal function).
Treatment received: current practice			
Proportion treated with timely GPD	10.8%	Demiralp et al (2019) ¹⁵ and BTG International Inc. sales data	Current GPD use estimated to be 18% of patients with delayed MTX elimination due to impaired renal function based on sales data. Assumed 60% of current GPD use was timely and 40% was delayed. ¹⁵
Proportion treated with delayed GPD	7.2%		
Proportion treated with hemodialysis	30.0%		
Proportion treated with SC alone	52.0%	N/A	Remainder of patients from above
GPD treatment			
GPD vials per patient	4	Assumption	Assumed based on recommended GPD dose being 50 Units per kg, with 1000 Units per vial. ¹¹ In the absence of data for different GPD doses, efficacy parameters are based on patients receiving 4 vials.
Efficacy			
Inpatient mortality: timely GPD	0.0%	Demiralp et al (2019) ¹⁵	Assumed the early GPD group (<72 hours) was equivalent to timely GPD, since time from admission was measured instead of time from HDMTX administration.
Inpatient mortality: delayed GPD	8.3%	Demiralp et al (2019) ¹⁵	
Inpatient mortality: hemodialysis	50.6%	Demiralp et al (2019) ¹⁵	
Inpatient mortality: SC alone	20.8%	Demiralp et al (2019) ¹⁵	In the absence of data for patients who specifically received SC without hemodialysis, the inpatient mortality for patients who received SC with or without hemodialysis (20.8%) was used.
Proportion of recovered patients who can rechallenge with, and complete, a full HDMTX regimen ^a	25.0%	Steward et al (2016) ⁷	Source reported proportion of adult patients with grades 3–4 AKI who continued their HDMTX dosing at the same level. Assumed this value was the same regardless of treatment received.

(Continued)

Table I (Continued).

Parameter	Value		Source		Notes	
Long-term survival (3-year OS) for patients who survive inpatient hospitalization ^b						
3-year OS for patients who completed full HDMTX regimen	85%		Singh et al (2022) ²¹		3-year OS for CNS lymphoma was derived from KM curves for patients who completed 5 HDMTX cycles and for those who did not. Assumed this data applied to adult patients. Median OS was not reached in the study for patients who completed HDMTX; extrapolations projected median OS beyond 10 years.	
3-year OS for patients who did not complete full HDMTX regimen	36%		Singh et al (2022) ²¹			
Average resource use ^c						
	Timely GPD	Delayed GPD	Hemo-dialysis	SC alone	Source	Notes
Hospital LOS (days) ^d	10.0	21.7	40.2	21.9 ^e	Demiralp et al (2019) ¹⁵	
ICU LOS (days) ^d	0.8	8.9	18.2	8.3	Demiralp et al (2019) ¹⁵	
Proportion on hemodialysis ^f	0.0%	13.0%	100.0%	0.0%	Assumption	
Leucovorin (mg/day)	1174 ^g	1174 ^g	1174 ^g	1174 ^g	Assumption	Assumed to be required for the duration of inpatient stay.
Fluid hydration (days)	10.0	21.7	40.2	21.9	Assumption	Assumed to be required for the duration of inpatient stay.
Urine alkalinization (hours)	240.0	520.8	964.8	525.6	Assumption	Assumed to be required for the duration of inpatient stay.
Plasma MTX tests (immunoassay) (per day)	1	1	1	1	Assumption	Assumed based on prescribing information for MTX. ¹²
Plasma MTX tests (HPLC) (total)	2 ^h	2 ^h	0	0	Prescribing information for GPD ¹¹	
Serum creatinine tests (per day)	1	1	1	1	Assumption	Assumed based on prescribing information for MTX. ¹²
Urine pH tests (per day)	4	4	4	4	Assumption	
Liver function tests (per day)	1	1	1	1	Assumption	
Costs						
GPD vial (1000 Units)	\$36,648.00 USD		BTG International Inc. WAC as of June 2022			
Leucovorin vial (200 mg)	\$10.00 USD		NAVLIN ²²		NDC 00143–9368-01.	
Hospitalization (toxicity, no hemodialysis; per day) ⁱ	\$3625.90 USD		Candrilli et al (2008) ²³		Inflated from \$25,638 over 12.2 days in 2004. Cost was derived from hospital charges using available cost-to-charge ratios.	

(Continued)

Table 1 (Continued).

Parameter	Value	Source	Notes
Hospitalization (toxicity, hemodialysis; per day) ⁱ	\$4374.20 USD	Candrilli et al (2008) ²³	Inflated from \$44,619 over 17.6 days in 2004. This cost factored in the average number of hemodialysis sessions required per patient. Cost was derived from hospital charges using available cost-to-charge ratios.
ICU (per day) ⁱ	\$7075.73 USD	Sanders et al (2021) ²⁴	Inflated from \$6285 per day in 2017. Cost was derived from hospital charges using available cost-to-charge ratios.
Fluid hydration (per day, ~8L)	\$27.68 USD	NAVLIN ²²	NDC 57896–0002-10.
Urine alkalinization (per 4 hours, 100 mL 8.4% sodium bicarbonate)	\$12.64 USD	NAVLIN ²²	NDC 72572–0740-20.
Plasma MTX test (immunoassay)	\$38.57 USD	CMS ²⁵	HCPCS 80204.
Plasma MTX test (HPLC)	\$278.30 USD	Mayo Clinic	Personal communication with information line.
Serum creatinine test	\$5.12 USD	CMS ²⁵	HCPCS 82565.
Urine pH test	\$3.58 USD	CMS ²⁵	HCPCS 83986.
Liver function test	\$15.50 USD	CMS ²⁵	84,450 (AST), 84,460 (ALT), 88,720 (bilirubin).

Notes: ^aIf a patient did not die during their inpatient stay, then it was assumed they eventually recovered from their delayed MTX elimination. The likelihood of HDMTX rechallenge (and completion of a full HDMTX regimen) was the same across survivors, regardless of treatment received. ^bIt was assumed that long-term survival data applied after the inpatient stay and initial treatment (ie, excluded patients who died during their inpatient stay). ^cIt was assumed that (1) daily SC was the same regardless of treatment and (2) SC and laboratory tests were required for the duration of inpatient stay and reflected LOS based on treatment received. ^dIt was assumed that hospital LOS values were the average for each treatment arm, reflecting longer or shorter stays based on recovery or experience of an AE. ^eIn the absence of data for patients who specifically received SC without hemodialysis, the LOS for patients who received SC with or without hemodialysis was used. ^fAll hemodialysis was assumed to be inpatient and all hemodialysis costs were assumed to be captured via the hospitalization cost per day with hemodialysis. It was assumed that the proportion of patients on hemodialysis could be used to determine whether to apply the hospitalization cost per day with hemodialysis versus no hemodialysis. ^gAssumed 81% of patients who received treatment for delayed MTX elimination due to impaired renal function would require HDLV and the remainder would receive LDLV. ²⁶ Assumed BSA for adults was 1.79 m². ²⁷ LDLV was assumed to be 10 mg/m² every 6 hours and HDLV was assumed to be 100 mg/m² every 3 hours. ²⁸ This resulted in low and high daily leucovorin doses of 72 mg and 1432 mg, respectively. If 81% require HDLV and 19% require LDLV, then the average daily dose is 1174 mg. ^hHPLC is required to accurately measure MTX concentrations in patients treated with GPD. ^{8,11} It was assumed that costs for hospitalization days included all other relevant costs (eg, nursing time, nephrologist consults, other tests, AEs).

Abbreviations: AE, adverse event; AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CMS, Centers for Medicare & Medicaid Services; CNS, central nervous system; GPD, glucarpidase; HCPCS, Healthcare Common Procedure Coding System; HDLV, high-dose leucovorin; HDMTX, high-dose methotrexate; HPLC, high-performance liquid chromatography; ICU, intensive care unit; KM, Kaplan-Meier; LDLV, low-dose leucovorin; LOS, length of stay; MTX, methotrexate; N/A, not applicable; NDC, National Drug Code; OS, overall survival; SC, supportive care; USD, United States dollars; WAC, wholesale acquisition cost.

Additional sensitivity analyses were conducted to assess the impact of changing the following model inputs: proportion of patients who experienced delayed MTX elimination due to impaired renal function following HDMTX, inpatient mortality rates, and hospitalization costs. All included sensitivity analyses and model inputs specific to these analyses are provided in Table 2.

Hypothetical Practical Scenarios

Two hypothetical practical scenarios were tested in the model to consider the real-world implications of changes in practice at US institutions. The first scenario involves an institution that sees three adult patients with delayed MTX elimination due to impaired renal function (of 50 treated with HDMTX) per year and does not stock glucarpidase or use hemodialysis. This scenario compares current practice of one patient treated with delayed glucarpidase to a hypothetical future practice treating either one or two patients with timely glucarpidase.

The second scenario involves an institution that sees five adult patients with delayed MTX elimination due to impaired renal function (of 100 treated with HDMTX) per year, maintains a stock of glucarpidase, and uses

Table 2 Changes to Model Inputs for Sensitivity Analyses

Sensitivity Analysis	Changes to Model Inputs
Base case	N/A
Pediatric population instead of adult population	<ul style="list-style-type: none"> Proportion with delayed MTX elimination due to impaired renal function changed to 1.8%. <ul style="list-style-type: none"> Source: proportion of osteosarcoma patients treated with HDMTX who developed nephrotoxicity (Widemann et al, 2004),²⁹ assuming all patients were pediatric. GPD vials per patient changed to 2. <ul style="list-style-type: none"> Assumed based on recommended GPD dose being 50 Units per kilogram, with 1000 Units per vial (BTG International Inc., 2019).¹¹ HDMTX rechallenge after recovery changed to 96.0%. <ul style="list-style-type: none"> Source: proportion of pediatric patients who received GPD and then continued HDMTX treatment (Svahn et al, 2017),³⁰ assuming patients who received GPD represented recovered patients. 3-year OS for patients who completed or did not complete full HDMTX regimen changed to 64% and 50%, respectively. <ul style="list-style-type: none"> Source: 3-year OS for patients who received HDMTX (Howard et al, 2019),³¹ assuming 5+ doses corresponded to HDMTX regimen completion, 1–2 doses corresponded to no HDMTX rechallenge, and data applied to pediatric patients. Proportion on hemodialysis for delayed GPD changed to 0.0%. <ul style="list-style-type: none"> Assumption. Leucovorin (mg/day) changed to 872 for each treatment option. <ul style="list-style-type: none"> Assumed BSA for pediatrics was 1.33 m² (GlobalRPh).³² LDLV was assumed to be 10 mg/m² every 6 hours and HDLV 100 mg/m² every 3 hours (Drugs.com).²⁸ This resulted in low and high daily leucovorin doses of 53 mg and 1064 mg, respectively. Assumed 81% of patients required HDLV and the remainder received LDLV (Flombaum et al, 2018).²⁶
Increased proportion with delayed MTX elimination	<ul style="list-style-type: none"> Proportion with delayed MTX elimination due to impaired renal function changed to 12.9% (Drost et al, 2017; Gros et al, 2022).^{4,5}
Decreased proportion with delayed MTX elimination	<ul style="list-style-type: none"> Proportion with delayed MTX elimination due to impaired renal function changed to 1.8% (Widemann et al, 2004).²⁹
Decreased inpatient mortality for treatment with hemodialysis or SC alone	<ul style="list-style-type: none"> Inpatient mortality for hemodialysis changed to 20.8% (ie, base case inpatient mortality for treatment with SC ± HDLV). Inpatient mortality for SC ± HDLV changed to 5.7% (Flombaum et al, 2018).²⁶
Decreased non-ICU hospitalization costs	<ul style="list-style-type: none"> Hospitalization cost (toxicity, no hemodialysis; per day) changed to \$1871.03. <ul style="list-style-type: none"> Calculated by applying the same proportional increase between the hospitalization cost for no toxicity and the cost for toxicity but no hemodialysis (Candrilli et al, 2008)²³ to an alternative hospitalization cost for no toxicity of \$1678.05 per day (Binder et al, 2020)³³ (inflated from \$1563.15 per day in 2019). Hospitalization cost (toxicity, hemodialysis; per day) changed to \$2257.16. <ul style="list-style-type: none"> Calculated by applying the same proportional increase between the hospitalization cost for no toxicity and the cost for toxicity and hemodialysis (Candrilli et al, 2008)²³ to the above \$1678.05 per day value (Binder et al, 2020).³³
Decreased ICU costs	<ul style="list-style-type: none"> ICU cost (per day) changed to \$5923.00 (Halpern and Pastores, 2015)³⁴ (inflated from \$4300 per day in 2010).

Abbreviations: BSA, body surface area; GPD, glucarpidase; HDLV, high-dose leucovorin; HDMTX, high-dose methotrexate; ICU, intensive care unit; LDLV, low-dose leucovorin; LOS, length of stay; MTX, methotrexate; N/A, not applicable; SC, supportive care.

hemodialysis. In this scenario, current practice sees two patients treated with timely glucarpidase and one with hemodialysis, and future practice increases the number of patients treated with timely glucarpidase to either four or all five patients. All included hypothetical practical scenarios are provided in [Table 3](#).

Table 3 Hypothetical Practical Scenarios for US Institutions

Hypothetical Current Practice	Hypothetical Change in Practice	Total Costs for Cohort		
		Hypothetical Current Practice	Hypothetical Change in Practice	Budget Impact
<ul style="list-style-type: none"> • Institution sees 50 adult patients treated with HDMTX per year, and three experience delayed MTX elimination due to impaired renal function.^a • Institution does not stock GPD and does not use hemodialysis for delayed MTX elimination due to impaired renal function. • In the past year, one patient was treated with GPD at 72 hours after the start of HDMTX infusion, and two patients received SC. 	<ul style="list-style-type: none"> • The one patient treated with GPD receives it earlier (within 60 hours). 	\$489,301	\$414,931	Cost savings of \$74,370
	<ul style="list-style-type: none"> • Two patients are treated with timely GPD and one is treated with SC. 		\$490,253	Additional cost of \$952
<ul style="list-style-type: none"> • Institution sees 100 adult patients treated with HDMTX per year, and five experience delayed MTX elimination due to impaired renal function.^b • Institution currently stocks GPD and uses hemodialysis for delayed MTX elimination due to impaired renal function. • In the past year, two patients were treated timely GPD, one with hemodialysis, and two received SC. 	<ul style="list-style-type: none"> • Four patients are treated with timely GPD and one receives SC. 	\$837,943	\$867,302	Additional cost of \$29,359
	<ul style="list-style-type: none"> • All five patients are treated with timely GPD. 		\$942,624	Additional cost of \$104,681

Notes: ^aAssumed 6% of HDMTX-treated patients had delayed MTX elimination due to impaired renal function to allow for round patient numbers in the hypothetical scenario. ^bAssumed 5% of HDMTX-treated patients had delayed MTX elimination due to impaired renal function to allow for round patient numbers in the hypothetical scenario.

Abbreviations: GPD, glucarpidase; HDMTX, high-dose methotrexate; MTX, methotrexate; SC, supportive care.

Results

For the base case analysis, of the 78 adult patients treated with HDMTX, a cohort of five patients was estimated to experience delayed MTX elimination due to impaired renal function. In the current practice scenario, only one patient received glucarpidase. Average costs per patient in the current practice scenario as compared with the proposed practice scenario are presented in [Figure 2](#). Hospitalization (ICU and non-ICU), SC, and monitoring costs were lower in the proposed practice scenario, whereas glucarpidase drug costs were higher. Across cost components, the largest differences between scenarios were for glucarpidase drug costs and ICU hospitalization costs. Proposed practice was associated with an increase of \$20,024 in costs per patient. The average per-patient cost was \$168,501 in the current practice scenario and \$188,525 in the proposed scenario. Considering all costs, proposed practice was associated with an increased total cost of \$99,959 for the cohort of five patients with delayed MTX elimination due to impaired renal function. The cost per patient (considering all cost categories) by treatment received was \$188,525 for timely glucarpidase, \$262,895 for delayed glucarpidase, \$234,487 for hemodialysis, and \$113,203 for SC ± HDLV ([Figure 3](#)).

Of patients with delayed MTX elimination due to impaired renal function, 31% required hemodialysis in the current practice scenario, but none required hemodialysis in the proposed practice scenario. The total hospital LOS (ICU and non-ICU) for the cohort was reduced by 80 days in the proposed glucarpidase use scenario (average of 16 fewer days per patient) compared with the current practice scenario. Total ICU LOS was reduced by 48 days (average of 10 fewer days per patient) in the proposed practice scenario. Total hospital (ICU and non-ICU) LOS and total ICU LOS for the cohort were 130 days and 52 days, respectively, in the current practice scenario and 50 days and 4 days, respectively, in the proposed practice scenario. The proportion of patients able to resume and complete HDMTX increased from 18% (current practice) to 25% (proposed practice) of patients. No patients died during inpatient treatment in the proposed practice scenario, whereas inpatient mortality was 27% in

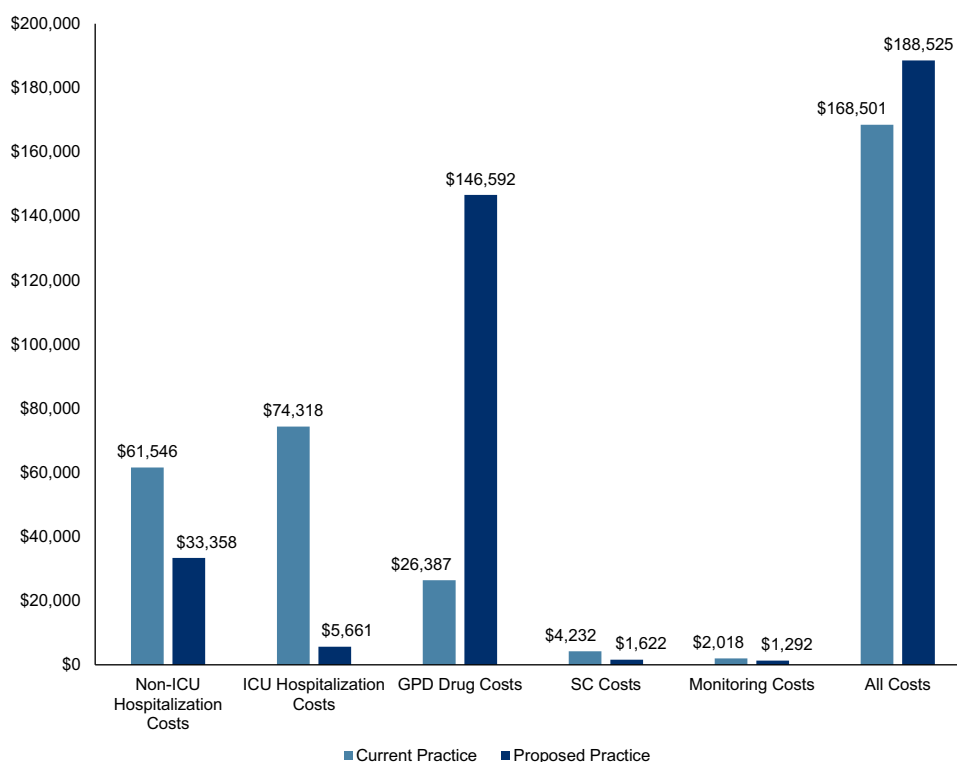


Figure 2 Average costs per patient (USD) associated with current practice (ie, fewer patients on GPD than indicated based on FDA label, with delayed or no administration in many patients) and proposed practice (ie, timely GPD administration for all eligible patients) scenarios for adult patients with delayed MTX elimination due to impaired renal function by each component of care.

Note: 'All costs' is a weighted average of costs shown in Figure 3.

Abbreviations: GPD, glucarpidase; ICU, intensive care unit; MTX, methotrexate; SC, supportive care; USD, United States dollars.

the current practice scenario. The proposed practice scenario was associated with an increase in long-term survival. The proportion of patients who survived after three years was 35% in the current practice scenario and 48% in the proposed practice scenario. The proposed practice scenario was associated with an additional cost per life saved of \$75,296, based on an incremental total inpatient cost of \$99,959 and incremental inpatient survival of 1.3 patients.

For outcomes per patient by treatment received, the average overall (ICU and non-ICU) hospital LOS was 10.0 days for timely glucarpidase, 21.7 days for delayed glucarpidase, 40.2 days for hemodialysis, and 21.9 days for SC \pm HDLV. The corresponding ICU LOS was 0.8 days, 8.9 days, 18.2 days, and 8.3 days, respectively. Inpatient survival by treatment received was 100% for timely glucarpidase, 92% for delayed glucarpidase, 49% for hemodialysis, and 79% for SC \pm HDLV. The corresponding 3-year survival was 48%, 44%, 24%, and 38%, respectively. After accounting for inpatient mortality, the proportion of patients who were able to rechallenge with HDMTX by treatment received was 25% for timely glucarpidase, 23% for delayed glucarpidase, 12% for hemodialysis, and 20% for SC \pm HDLV.

Results of sensitivity analyses are provided in Figure 4. For the analysis considering pediatric patients, total costs for the cohort and average costs per patient were lower compared with adults (ie, the base case analysis), and cost savings of \$3444 per patient were achieved with proposed practice compared with current practice. Proposed glucarpidase use was also consistently associated with improved clinical outcomes in this patient group.

Results of two hypothetical practical scenarios are provided in Table 3. For the first scenario, changing from current practice of one patient treated with delayed glucarpidase to either one or two patients treated with timely glucarpidase was associated with a cost savings of \$74,370 and an additional cost of \$952, respectively, for the institution. For the second scenario, changing from current practice of two patients treated with timely glucarpidase and one with



Figure 3 Average costs per patient (USD) for adult patients with delayed MTX elimination due to impaired renal function based on treatment received.

Abbreviations: GPD, glucarpidase; HDLV, high-dose leucovorin; MTX, methotrexate; SC, supportive care; USD, United States dollars.

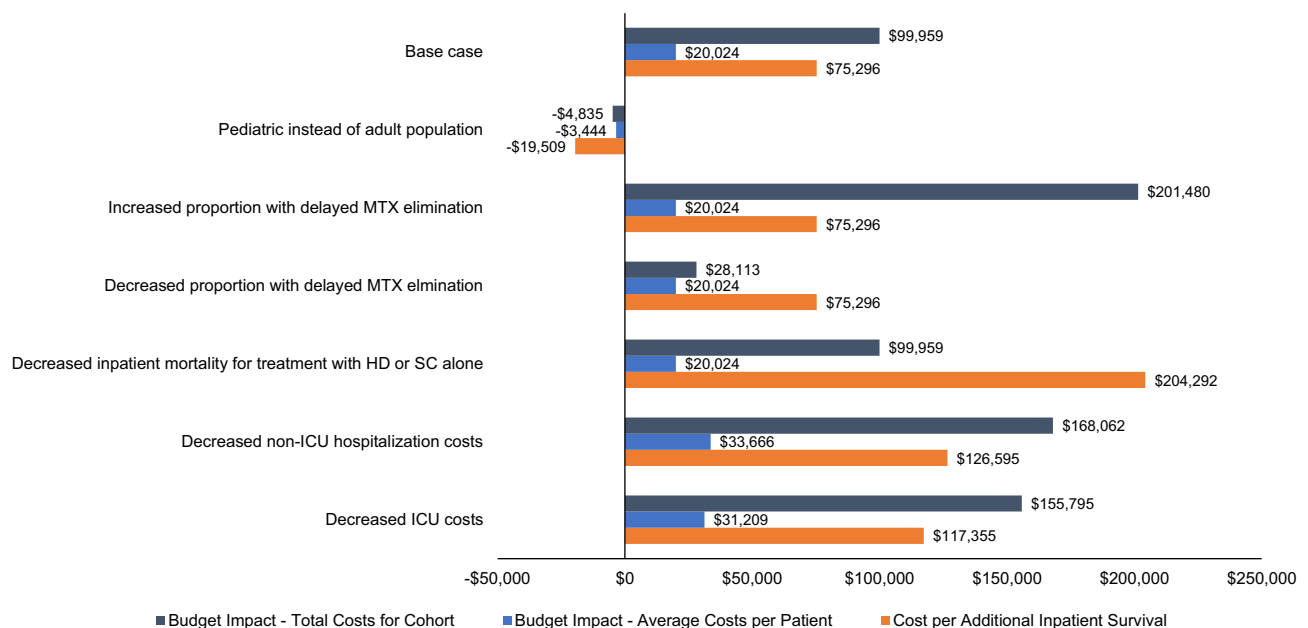


Figure 4 Variation in treatment costs (USD) associated with sensitivity analyses described in Table 2. Note: Budget impact refers to the cost difference in switching from current practice to proposed practice.

Abbreviations: HD, hemodialysis; ICU, intensive care unit; MTX, methotrexate; SC, supportive care; USD, United States dollars.

hemodialysis to either four or all five patients treated with timely glucarpidase was associated with an additional cost of \$29,359 and \$104,681, respectively, for the institution.

Discussion

This economic analysis considered the estimated clinical and cost outcomes for adult patients in the US who received treatment for delayed MTX elimination due to impaired renal function, for the mix of treatments used in current practice as compared with proposed practice.

Enabling timely access to glucarpidase for all eligible patients was associated with a cost increase per patient of 12% relative to the average per-patient cost in the current practice scenario, while at the same time increasing patient survival, decreasing the number of patients who require hemodialysis, increasing the opportunity for HDMTX rechallenge, and reducing hospital LOS. A reduction in hospital LOS will additionally help to free up resources for other patients, and so is associated with increased economic opportunity. There are many factors to consider in therapeutic decision-making, including, but not limited to, the costs and clinical outcomes discussed herein. For each patient with delayed MTX elimination due to impaired renal function, timely treatment with glucarpidase resulted in cost savings compared with hemodialysis or delayed glucarpidase. Treatment with glucarpidase had an incremental cost versus SC alone but was associated with substantially improved clinical outcomes. Timely treatment with glucarpidase resulted in decreased hospital costs, which helped offset drug acquisition costs.

It was not possible to perform a full analysis of pediatric patients based on currently available data. Nonetheless, a sensitivity analysis was possible using the risk of delayed MTX elimination due to impaired renal function and the likelihood of HDMTX rechallenge and 3-year OS for a pediatric population, using drug doses appropriate for this group, and assuming they are not treated with hemodialysis. Other model inputs were the same as those used for the base case analysis in adult patients. The results of this sensitivity analysis suggest that for pediatric patients, shifting to proposed glucarpidase use not only improves patient outcomes but also results in cost savings.

The impact of minimal shifts in treatment patterns to improve patient outcomes on institution costs was demonstrated for two hypothetical practical scenarios anticipated to be relevant to US institutions. First, moving from one patient treated with delayed glucarpidase to one patient treated with timely glucarpidase resulted in cost savings; moving to two patients being treated with timely glucarpidase was associated with a very minimal additional cost. Second, moving from two patients treated with timely glucarpidase and one with hemodialysis to four or all five patients treated with timely glucarpidase was associated with additional costs that were relatively small compared to the cost for the institution. For example, the \$29,359 additional cost for four patients treated with timely glucarpidase represents a cost increase of only 3.5%.

There were a few limitations to note for this simulation. First, limited data were available to inform model inputs, necessitating a variety of assumptions. Where data were limited, similar assumptions were made across treatment arms to not bias the model results. A key source of model inputs was a study of Medicare claims data by Demiralp and colleagues (2019),¹⁵ which, while valuable as a reflection of real-world experience (in that it represents the true variability observed in clinical practice, and captures different cancer types, MTX dosing regimens, and supportive care practices), was impacted by challenges shared by all retrospective database analyses, such as missing data and potential inconsistency in reporting diagnosis of MTX-associated kidney injury. Second, the inherent simplicity of decision tree models constrained the scope and complexity of this analysis; simulated results aim to present an average patient and facility experience, but do not capture patient-to-patient nuances. However, the use of this modeling approach was appropriate given the type of data that were available, the short-term time horizon, and the research question. Finally, the model did not include parameters for individual AEs, as AE-associated costs were assumed to be captured within the hospitalization costs. This approach may have resulted in an underestimation of the benefits associated with proposed glucarpidase use given that (1) timely glucarpidase may reduce long-term AEs requiring readmission, such as mucositis, and (2) hemodialysis may lead to specific severe AEs not expected for other treatment approaches (eg, catheter exit site bleeding, electrolyte imbalances, stroke, arrhythmias).²⁰

Study strengths included the use of conservative assumptions expected to bias against the economic value of glucarpidase and the inclusion of sensitivity analyses using published alternative data sources to assess the robustness

of model results to changes in key inputs. To our knowledge, this is the first economic analysis to consider the costs and clinical outcomes associated with the use of glucarpidase and other treatments for delayed MTX elimination due to impaired renal function in the US.

Additional analyses would be helpful to build on this analysis and consider other patient populations by age, cancer type, and geographical location, as well as different model perspectives (eg, considering societal impacts/patient-borne costs). However, given the data limitations encountered in this analysis, future analyses would benefit from additional studies aimed at generating relevant data for key model inputs. For example, there was a paucity of mortality and resource use data specific to pediatric patients, which necessitated using data for adult patients in this sensitivity analysis.

Conclusions

For adult patients in the US with delayed MTX elimination due to impaired renal function, shifting from current practice to all eligible patients receiving treatment with glucarpidase within 60 hours (ie, proposed practice) was estimated to be associated with a cost increase per patient of \$20,024 and an additional cost per life saved of \$75,296, while improving patient outcomes substantially. In the simulation, timely treatment with glucarpidase resulted in a cost savings of \$74,370 and \$45,962 per patient compared to delayed glucarpidase treatment or treating with hemodialysis, respectively, but was more expensive than SC alone, without considering the additional reimbursement that may be associated with glucarpidase use.

Abbreviations

AE, adverse event; AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CMS, Centers for Medicare & Medicaid Services; CNS, central nervous system; FDA, Food and Drug Administration; GPD, glucarpidase; HCPCS, Healthcare Common Procedure Coding System; HDLV, high-dose leucovorin; HDMTX, high-dose methotrexate; HPLC, high-performance liquid chromatography; ICU, intensive care unit; KM, Kaplan-Meier; LDLV, low-dose leucovorin; LOS, length of stay; MTX, methotrexate; N/A, not applicable; NDC, National Drug Code; OS, overall survival; SC, supportive care; US, United States; USD, United States dollars; WAC, wholesale acquisition cost.

Ethics Statement

Institutional review board or ethics committee approval was not required for this study because it was a pharmacoeconomic modeling study that did not involve patient contact and used aggregated anonymized data from other studies.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

J. Kala and R. Nelson have received compensation for serving as a consultant or speaker for BTG International Inc. C. Drudge, A. Zhou, and M. Bourque are employees of EVERSANA, which has provided paid consulting services to BTG International Inc. S. Ward is an employee of BTG International Inc. The authors report no other conflicts of interest in this work.

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