Therapeutic drug monitoring and selective use of Glucarpidase in High-dose Methotrexate therapy: A cost analysis from the Algerian payer perspective

EE 731

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INTRODUCTION

Malignant hematologic diseases encompass cancers originating from hematopoietic tissue or lymphoid organs, primarily leukemias and lymphomas. In Algeria, leukemia accounted for 1,731 new cases in 2022, while non-Hodgkin lymphomas represented 2,226 new cases the same year (1,2). High-dose methotrexate (**HD-MTX, ≥500 mg/m²**) is a cornerstone in the treatment of these malignancies. However, delayed elimination of MTX-HD may lead to severe hematological toxicities, including neutropenia and thrombocytopenia (3).

Therapeutic drug monitoring (**TDM**) of HD-MTX is therefore essential to guide folinic acid rescue and mitigate adverse effects. Managing chemotherapy-induced toxicities imposes a substantial economic burden; in the United States, the cost of febrile neutropenia can reach up to 49,917 USD (4). Glucarpidase offers an alternative in cases of delayed MTX elimination, achieving >97% plasma MTX reduction within 24 hours (5). Yet, its high cost raises critical cost-effectiveness concerns for health systems.

OBJECTIVE

This study aims to highlight the value of HD-MTX TDM, estimate the annual cost of treating malignant hematologic diseases with HD-MTX at the Central Army Hospital (CAH, Algiers), and assess the budget impact of introducing glucarpidase in cases of MTX overexposure.

METHOD

a. Study design and population

A 12-month observational study (May 2024–May 2025) was conducted at the Toxicology Laboratory, CAH. Adult patients (>18 years) with acute leukemia or non-Hodgkin lymphoma treated with at least one cycle of HD-MTX were included. Patients with incomplete records or treated before May 2024 were excluded.

b. HD-MTX Therapeutic Drug Monitoring

Plasma MTX levels were measured at 24h (and when required at 48h, 72h…) using EMIT on VIVA-E® SIEMENS. Overexposure was defined as >10 µmol.L^{-1} (H24), >1 µmol.L^{-1} (H48), or >0.1 µmol.L^{-1} beyond H72. (6)

c. Pharmacoeconomic evaluation

Medical records of 24 patients (59 cycles) were reviewed to estimate the **economic burden**. Direct hospital costs included hospitalization, laboratory and imaging tests, drugs (HD-MTX, hydration, folinic acid rescue), and toxicity management.

A **budget impact model** (Excel 2019) simulated in overexposed patients (MTX48h>10 µmol.L^{-1}) :

- ***Standard management*** (folinic acid rescue, prolonged hospitalization, toxicity costs).
- ***Management with glucarpidase*** (fixed 1000 U dose (7), shorter hospitalization, fewer tests).

Costs were estimated in DZD and converted into USD using June 2025 exchange rates.

d. Statistical analysis

Data were analyzed with IBM SPSS, Version 30.0 (IBM Corp., Armonk, NY, USA).

RESULTS AND DISCUSSION

a. Study design and population

Table 1. Baseline characteristics of the study population

Characteristic	Value
Sex	
Male, n (%)	12 (50)
Female, n (%)	12 (50)
Age (years)	
n (%)	24 (100)
Mean ± SD	54.33 ± 17.01
[Min – Max]	[24 – 89]
Weight (kg)	
n (%)	22 (91.7)
Mean ± SD	65.91 ± 14.77
[Min – Max]	[50 – 106]
Body Surface Area (m²)	
n (%)	20 (83.3)
Mean ± SD	1.73 ± 0.19
[Min – Max]	[1.41 – 2.06]
Type of hematologic malignancy	
NHL, n (%)	19 (79.2)
ALL, n (%)	5 (20.8)
MTX-HD dose (g) Median (Min – Max)	5.0 (2.0 – 6.0)

b. MTX-HD Therapeutic Drug Monitoring

A total of **153 MTX plasma assays** were performed. Among the 48h samples, **17.95%** (7/39 with MTX H48 >1 µmol/L) were in the toxic range, compared to **55.81%** (24/43 with MTX H72 >0.1 µmol/L).

Table 2. Residual MTX concentrations at different times post MTX-HD chemotherapy.

Table 3. Biological parameters before and after MTX-HD chemotherapy.

c. Pharmacoeconomic Evaluation

- ***Estimation of the Economic Burden of Malignant Hemopathies***

The economic burden was estimated at $100,209.79, based on direct medical costs distributed across several expenditure items: therapeutic protocols including high-dose MTX administration, management of toxicities, laboratory investigations, and hospitalization (**Figure 1 & 2**).

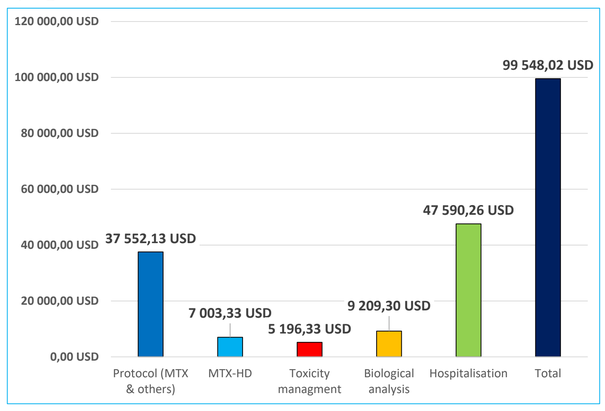

Figure 1. Economic burden of the management of malignant hemopathies at HCA: analysis from May 2024 to May 2025.

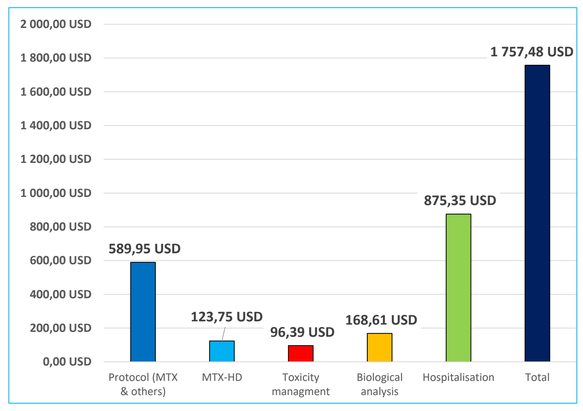

Figure 2. Economic burden of the management of malignant hemopathies: analysis of cost items per patient.

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Figure 3. A **103.8% increase** in total cost was observed in patients with MTX H48 > 1 µmol/L under standard management, highlighting the major economic burden of treatment-related complications. Similar findings by ***Mejía-Aranguré et al.*** showed that, during induction therapy for ALL, the cost of adverse events could equal that of chemotherapy itself. (8)

- ***Budget impact simulation of glucarpidase use (***S2-S1 → **+585.05%)**

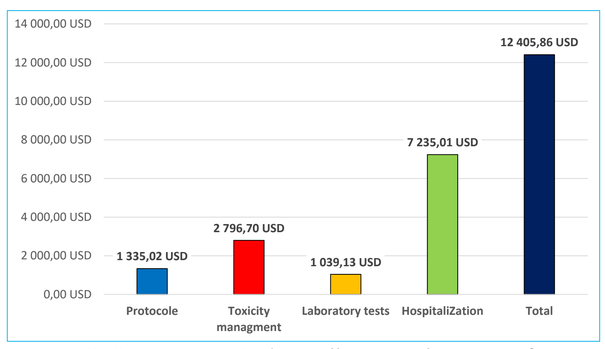

Figure 3. Scenario 1: Budget Allocation by Type of Expenditure.

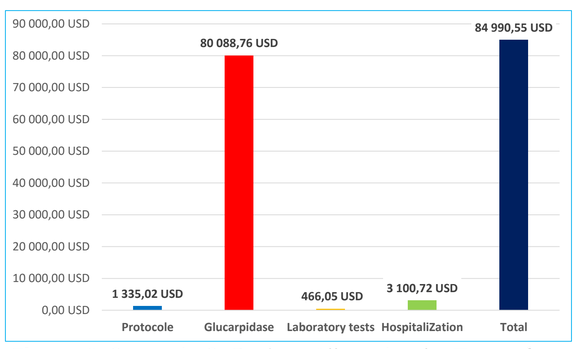

Figure 4. Scenario 2: Budget Allocation by Type of Expenditure.

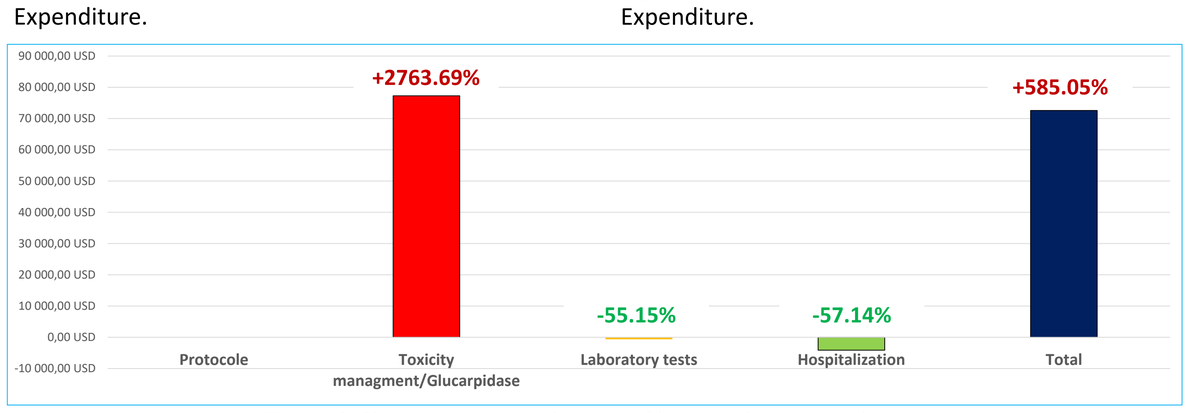

Figure 4. Simulated budget impact of introducing glucarpidase.

The comparison of both scenarios shows a major cost redistribution. With glucarpidase, hospitalization (–$4,134.9) and laboratory costs (–$573.1) decrease due to improved toxicity management, but the **high drug price** raises the total cost to $72,582.9. This reflects a proactive strategy: higher upfront spending to prevent complications, shorten hospital stays, and enhance safety. The **+585.08%** increase here far exceeds that of ***Kala et al. (2023, +12%),*** due to differences in context and cost scope (9). Weight-based dosing (50 IU/kg) would push costs to $243,060.2 (+1,959.78%), though ***Arjen et al. (2025)*** argue this is unnecessary since a fixed single-vial dose is both effective and cost-saving (7). Sensitivity analysis confirms glucarpidase's cost as the key driver of expenditures and a potential budget imbalance factor.

CONCLUSION

TDM of HD-MTX is essential to prevent severe toxicities and optimize individualized dosing. Glucarpidase, though costly, offers a valuable option in critical cases to preserve renal function and avoid major complications. A balanced evaluation of costs versus clinical and organizational benefits is needed for its integration into healthcare systems.

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CONTACT

REFERENCES