COMPARISON OF TWO PROTOCOLS FOR THE ADMINISTRATION OF LEUCOVORIN RESCUES AFTER HIGH DOSE METHOTREXATE INFUSION OF 24 HOURS

Escolà-Rodríguez A[1], Arranz Pasqual N[1], Bastida C[1], Albanell M[1], Monge Escartín I[1], Maté Arbaiza P[1], Ruiz Boy S[1], Carcelero San Martín E[1], Soy Muner D[1]

[1]Pharmacy Service. Division of Medicines. Hospital Clínic de Barcelona - Universitat de Barcelona

Background and Importance

- Therapeutic drug monitoring (TDM) of methotrexate (MTX) in plasma is a standard procedure to early identify patients with delayed drug elimination and adjust leucovorin dose.
- Leucovorin rescues should start within 42-48 hours of the beginning of high dose (HD)-24h-MTX infusion to avoid MTX toxicity, but extending leucovorin rescues more than needed can reduce MTX antitumor effect.

Aim and Objectives

- **Primary outcome:** to assess whether the implementation of the new protocol allowed reducing the total leucovorin dose administered after HD-24h-MTX infusion.
- **Secondary outcomes:** compare the incidence of nephrotoxicity and the level of compliance of appropriate MTX sampling times and leucovorin rescues between both protocols.

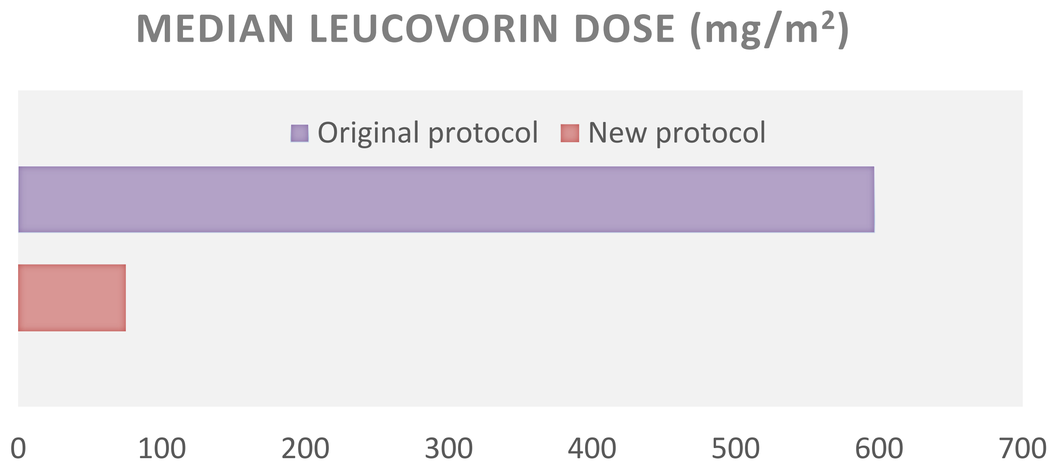
Materials and Methods

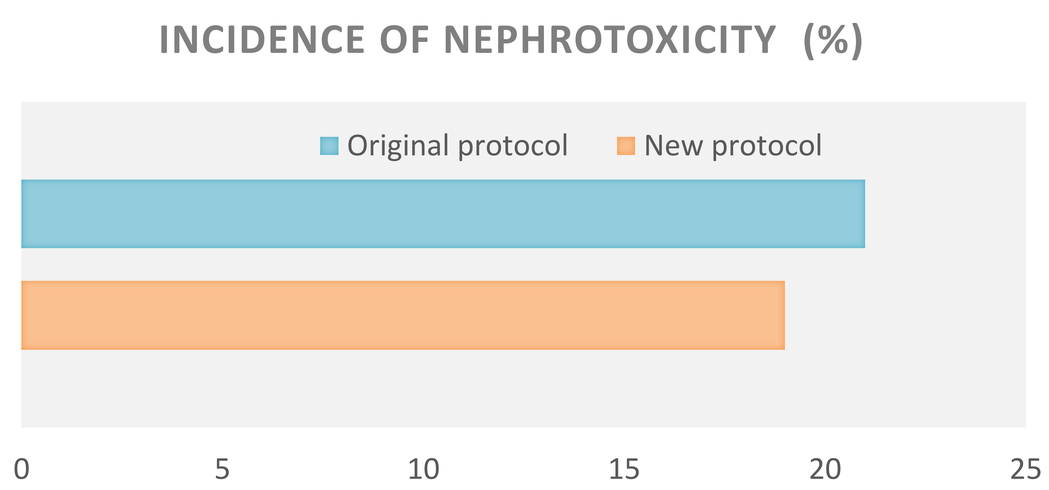
- **Retrospective observational study** conducted in a tertiary university hospital from May 2019 to June 2022.
- **Inclusion criteria:** adults treated with a HD-24h-MTX infusion as treatment for acute lymphoblastic leukemia (ALL) and Burkitt lymphoma (LB). Patients were stratified (1:1) according to the following protocol.
- **Data collected were:** age, sex, hematology malignancy, MTX dose, leucovorin rescues and serum creatinine.
- MTX plasma concentration were determined:
  - **Original protocol:** 48 hours after infusion completion.
  - **New protocol (based on PETHEMA-2019 protocol):** 12, 23, 36, 42 and 60 hours from the start of MTX infusion. MTX plasma determinations at 12, 23 and 36 hours were used to predict 42 hours MTX concentration using a population PK model.

Results

Table 1. Clinical and demographic characteristics of the study population

	Original protocol	New protocol
HD-24h-MTX infusions (n)	29	29
Patients (n)	20	20
Sex (% males)	65%	75%
Age (Mean±SD), years	49 ± 16	49 ± 15
Diagnosis	10 LB 7 ALL-B 3 ALL-T	7 LB 11 ALL-B 2 ALL-T
Median [IQR] leucovorin dose (mg/m^2)	597 [475, 700]	75 [45, 180]
Nephrotoxicity (%)	21%	19%
Correctly drawn TDM sample extractions (%)	97%	93%
Correct administration of leucovorine rescue (%)	55%	76%





- The median [IQR] **leucovorin dose** administered per cycle following the **new protocol was an 87% lower** than the dose administered with the original protocol (p<0.001).
- The incidence of **nephrotoxicity** (increase of >0.3mg/dL of baseline creatinine) was **3% lower following the new protocol** (p=0.84).

Conclusion and Relevance

The implementation of the new protocol allowed a **significant reduction of the leucovorin dose by 87% without an increase in nephrotoxicity.** Model-based dose optimization based on TDM is feasible for patients under HD-24h-MTZ infusion. Nevertheless, measures to increase adherence to the new protocol may be implemented.