Nederlandse Ziekenhuisfarmacie-dagen 2024

De hier opgenomen abstracts vormen een selectie, namelijk de drie best beoordeelde abstracts, uit de presentaties tijdens de Nederlandse Ziekenhuisfarmaciedagen op 28 en 29 november 2024 te Arnhem. De digitale versie van deze publicatie op www.npfo.nl bevat alle gepresenteerde abstracts.

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ASSOCIATION OF BUSULFAN EXPOSURE AND OUTCOMES AFTER HCT FOR PATIENTS WITH AN INBORN ERROR OF IMMUNITY

Tim Bognàr [a†*], **Moises Garcia** [b†], **Arief Lalmohamed** [ac], **Tayfun Güngör** [d], **Mathias Hauri-Hohl** [d], **Susan Prockop** [e], **Layne Oram** [e], **Sung-Yun Pai** [ef], **Jordan Brooks** [g], **Rada M. Savic** [g], **Christopher C. Dvorak** [g], **Janel R. Long-Boyle** [g], **Maja Krajinovic** [h], **Henrique Bittencourt** [h], **Anne-Charlotte C. Teyssier** [h], **Yves Théoret** [h], **Cary Martinez** [i], **Toine C.G. Egberts** [ac], **Erin Morales** [i], **Mary Slatter** [j], **Geoffrey D.E. Cuvelier** [k], **Robert Chiesa** [l], **Robert F. Wynn** [m], **Mary Coussons** [m], **Maria P. Cicalese** [nop], **Marc Ansari** [qr], **Susan E. Long** [s], **Christen L. Ebens** [s], **Hannah Lust** [t], **Sonali Chaudhury** [t], **Christa E. Nath** [u], **Peter J. Shaw** [u], **Steven J. Keogh** [u], **M.Y. Eileen C. van der Stoep** [vwx], **Robbert Bredius** [v], **Caroline A. Lindemans** [yz], **Jaap-Jan Boelens** [b†] and **Imke H. Bartelink** [a1a2†]

[a] Department of Clinical Pharmacy, University Medical Center Utrecht/Wilhelmina Children's Hospital, Utrecht.
[b] Cell Transplantation and Cellular Therapies, Memorial Sloan-Kettering Cancer Center, New York, United States.
[c] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University.
[d] Division of Stem Cell Transplantation and Children's Research Center, University Children's Hospital Zurich, University of Zürich, Zürich, Switzerland.
[e] Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, United States.
[f] Center for Cancer Research, National Cancer Institute (NCI), National Institutes of Health (NIH), United States.
[g] Departments of Allergy/Immunology/Bone Marrow Transplantation, Clinical Pharmacy, or Bioengineering & Therapeutic Sciences of the University of California San Francisco (UCSF), SanFrancisco, United States.
[h] Centre de Cancérologie Charles-Bruneau Centre de recherche - Hospital Sainte-Justine Montréal, Québec, Canada.
[i] Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital, Texas, United States.
[j] Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, United Kingdom
[k] Pediatric Blood and Marrow Transplantation, CancerCare Manitoba, University of Manitoba, Manitoba, Canada
[l] Great Ormond Street, Hospital for Children & Stem Cell Program, London, United Kingdom.
[m] Department of Blood and Marrow Transplant, Royal Manchester Children's Hospital, Manchester, United Kingdom.
[n] San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), IRCCS San Raffaele Scientific Institute, Milan, Italy.
[o] Faculty of Medicine and Surgery, Vita-Salute S. Raffaele University, Milan, Italy.
[p] Pediatric Immunohematology and Bone Marrow Transplantation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy.
[q] Cansearch Research Platform in Pediatric Oncology and Hematology, Faculty of Medicine, Department of Pediatrics, Gynecology and Obstetrics, University of Geneva, Geneva, Switzerland.
[r] Division of Pediatric Oncology and Hematology, Department of Women, Child and Adolescent, University Geneva Hospitals, Geneva, Switzerland.
[s] Division of Pediatric Blood and Marrow Transplant & Cellular Therapy, MHealth Fairview Masonic Children's Hospital, University of Minnesota, Minneapolis, United States.
[t] Stem Cell Transplant Program, Ann & Robert Lurie Children's Hospital/Northwestern University, Chicago, United States.
[u] Children's Hospital at Westmead, Sydney, Australia.
[v] Department of Pediatrics, Willem Alexander Children's Hospital, Leiden University Medical Center.
[w] Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center.
[x] Center for Cell and Gene Therapy, Leiden University Medical Center.

[y] Department of Pediatrics, UMC Utrecht.
[z] Princess Máxima Center, Utrecht.
[a1] Amsterdam University Medical Center, Location VUmc, Amsterdam.
[a2] Cancer Center Amsterdam, Imaging and Biomarkers, Amsterdam.
† Authors have contributed equally.

* Correspondence: t.bognar-2@umcutrecht.nl.

Background

Previously, a clear relation between cumulative busulfan exposure (AUC) and clinical outcomes after pediatric and young adult allogeneic hematopoietic cell transplantation (HCT) was shown. As these studies involved only a small number of patients with inborn errors of immunity (IEI), the optimal target for this group remains unclear.

Objective

The objective of this study was to assess the optimal busulfan exposure in pediatric and young adult IEI patients.

Methods

Patients who received a busulfan-based conditioning regimen between 2000 and 2023 from 17 centers were included. Our main outcome of interest was event-free survival (EFS); events considered were graft-failure (GF), and mortality. Other outcomes of interest were the most recent (myeloid or whole blood) donor chimerism. Patients were categorized into 4 IEI subgroups: combined immunodeficiency (CID), severe combined immunodeficiency (SCID), neutrophil disorders and hemophagocytic lymphohistiocytosis (HLH)-related disorders. Busulfan exposure was calculated by individual centers (AUCCENTER) and was re-estimated using all raw concentration-time profiles with nonlinear mixed effect modeling (AUCNONMEM) by applying an externally validated busulfan pharmacokinetic (PK) model (Bartelink, 2012). To assess the validity of the AUC prediction among centers, we compared the AUCCENTER with AUCNONMEM. To evaluate the busulfan AUCNONMEM in relation with the outcomes of interest, we used propensity score adjusted Weibull survival functions and Fine-Gray competing risk regression.

Results

Overall, 562 patients were included: 154 (27.4%) SCID, 173 (30.8%) CID, 101 (18.0%) HLH and
134 (23.8%) neutrophil disorders. Median age was 1.7 years (range 0.08-27.0). CID disease subtype was an effect modifier (P = 0.03), therefore, patients with SCID, HLH-related, and neutrophil disorders were analyzed together (n = 389). The

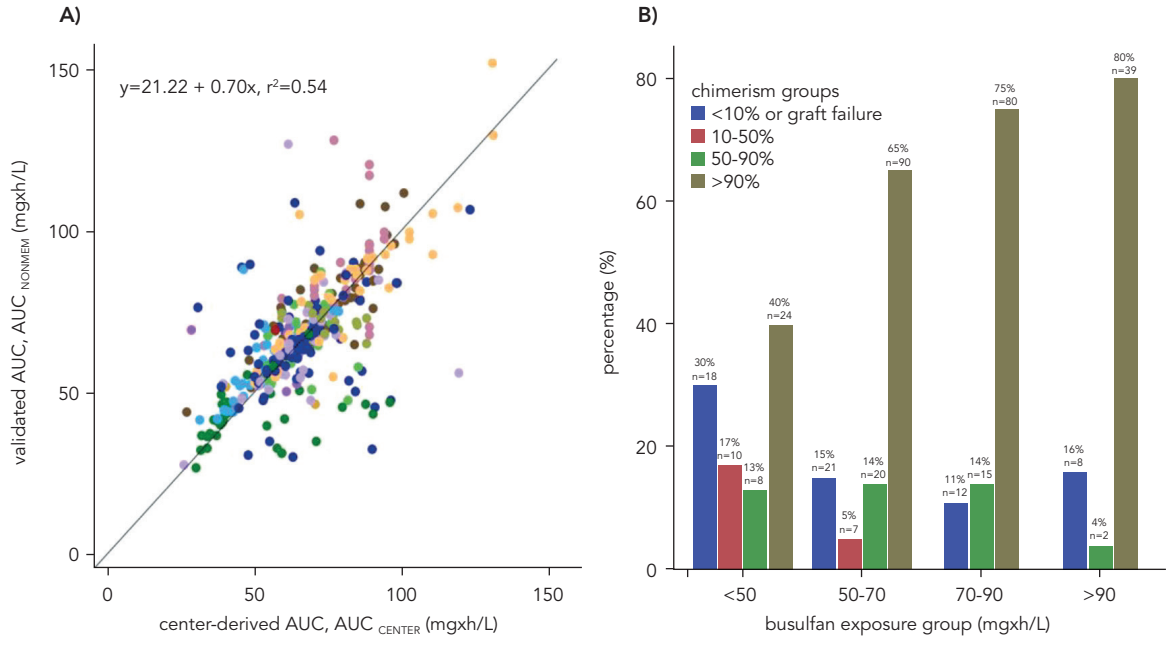

Figure 1. **A)** The busulfan exposure calculated by the centers (AUC_{CENTER}) versus the exposure estimation using a validated pharmacokinetic model (AUC_{NONMEM}; centers denoted by color), **B)** donor chimerism stratified by AUC subgroups.

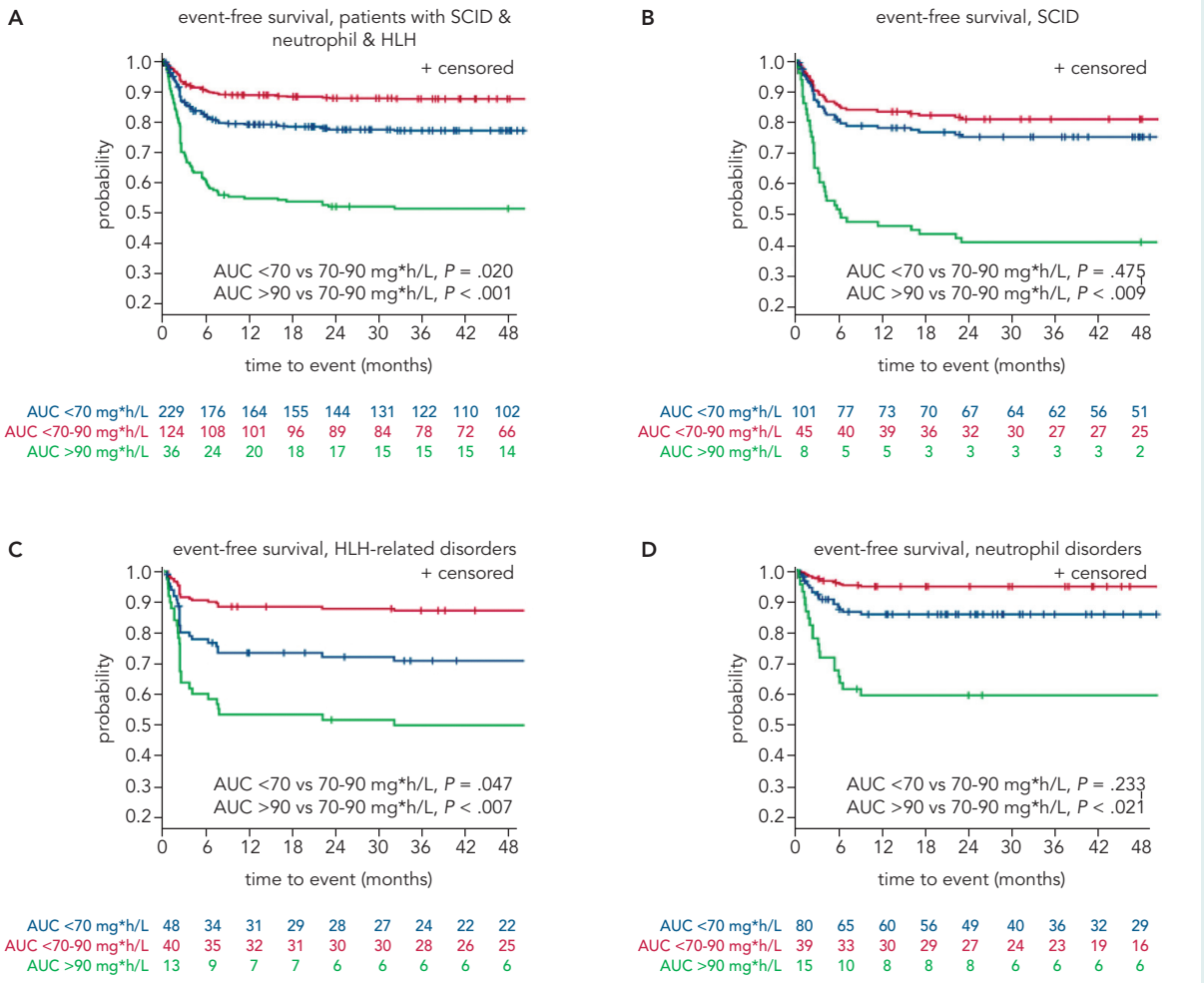

Figure 2. Propensity score-adjusted Fine-Gray Kaplan-Meier plots of event-free survival stratified for 3 AUC busulfan exposure groups (<70, 70-90, and >90 mg × h/L). Patients with (A) SCID, HLH-related, and neutrophil disorders, (B) SCID, (C) HLH-related, and (D) neutrophil disorders.

median busulfan AUCNONMEM was 69.0 mg×h/L and correlated poorly with AUCCENTER (r^2 = 0.54; Figure 1A). In patients with the found optimal busulfan AUCNONMEM of 70-90 mg×h/L, 2-year EFS was 87.9% (95% confidence interval [CI] 80.3-92.6%), superior to < 70 mg×h/L (adjusted hazard ratio [HR] 1.97, 95% CI 1.11-3.49, P = 0.02), and > 90 mg×h/L (adjusted HR 5.05, 95% CI 2.43-10.49, P < 0.0001, Figure 2A-D). Donor chimerism increased with higher busulfan AUCNONMEM, plateauing at 90 mg×h/L (Figure 1B). For CID patients, an optimal AUCNONMEM for donor chimerism was found to be > 70 mg×h/L, while no optimal AUCNONMEM for EFS > 50 mg×h/L was found.

Conclusions

Improved EFS and higher donor chimerism may be achieved by targeting a cumulative busulfan AUCNONMEM of 80 mg×h/L (range 70-90). The data stresses the importance to uniformly use a validated population PK-model to estimate the AUCNONMEM.

De abstractpresentatie van Tim Bognàr werd bekroond met de prijs voor Best Abstract 2024.

DOSE-DEPENDENT RELATIONSHIPS IN PRESCRIBING CASCADES: A COHORT STUDY

Ruveyda Gündogan-Yilmaz [a]*, **Sadaf Wahedi** [a], **Johanna H.M. Driessen** [bc], **Atiya Mohammad** [ad], **Petra Denig** [d] and **Fatma Karapinar** [abc]

[a] Department of Clinical Pharmacy, OLVG, Amsterdam.
[b] Department of Clinical Pharmacy & Toxicology, Maastricht University Medical Center+.
[c] Department of Clinical Pharmacy, CARIM, Cardiovascular Research Institute Maastricht, Maastricht University.
[d] Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen.

* Correspondence: ruveyda_yilmazz@hotmail.com.

Background

Prescribing cascades occur when new so-called marker medications are prescribed to treat adverse drug reactions (ADRs) caused by an initial medication (index). This can lead to polypharmacy and increased healthcare costs. While dose reduction is often suggested as a strategy to mitigate prescribing cascades, the extent to which the dosage of an index medication affects the development of these cascades remains unknown.

Objective

This study aimed to investigate the dose-dependence of prescribing cascades across a range of medications.

Methods

We performed a cohort study using prescription sequence symmetry analysis (PSSA) with data from over 600 Dutch community pharmacies. The relationship between different doses of index medications and the occurrence of 18 prescribing cascades was examined, including ACE inhibitors (ACEIs), statins, proton pump inhibitors (PPIs), diuretics, and antidepressants. Dose categories were determined using the World Health Organization (WHO) defined daily dose (DDD) classification, divided into low (< 0.50 DDD), medium (≥ 0.50 and ≤ 1.50 DDD), and high (> 1.50 DDD) dose groups. Adjusted sequence ratios (aSRs) were calculated, with an aSR greater than 1 indicating the occurrence of a prescribing cascade. A dose-dependent relationship was confirmed when aSRs increased with higher doses and their 95% confidence intervals (CIs) did not overlap.

Results

Of the 18 cascades analyzed, 12 showed a dose-dependent relationship. Notably, all seven ACEI-related cascades displayed a dose-dependent relationship. The aSR for ACEI-induced cough followed by antitussives increased from 2.09 (95% CI: 1.95-2.23) in the low-dose group to 2.75 (95% CI: 2.67-2.83) in the high-dose group. Similarly, for ACEI-induced cough followed by inhaled adrenergics, the aSR increased from 0.86 (95% CI: 0.71-1.00) in the low-dose group to 1.51 (95% CI: 1.44-1.59) in the high-dose group (Figure 1). Statins also exhibited dose-dependency in three of the six cascades. In contrast, no dose-response relationship was observed for cascades involving PPIs and diuretics.

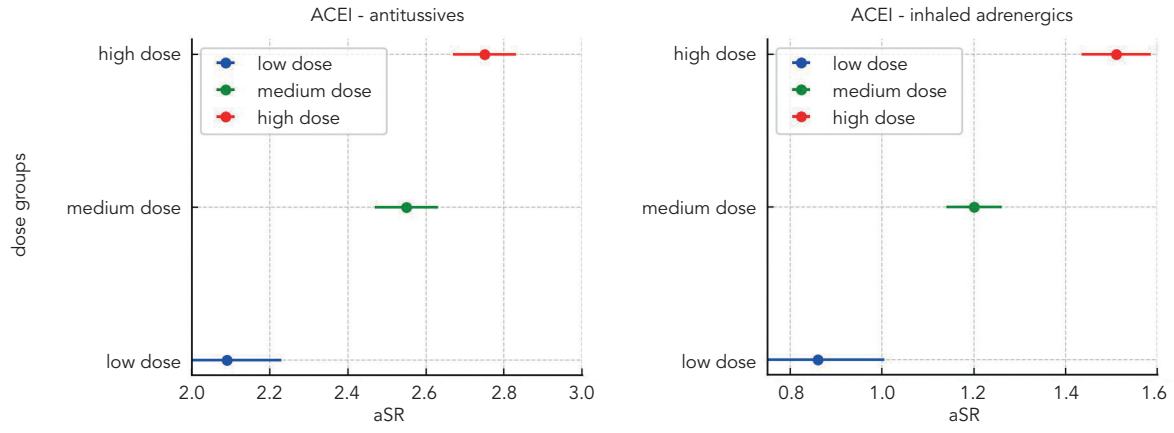

Figure 1. Each plot displays the adjusted sequence ratio (aSR) for low, medium, and high doses with confidence intervals. An increasing aSR with higher doses, without overlapping confidence intervals, indicates a dose-dependent relationship.

Conclusions

These findings underscore the importance of dosage in managing prescribing cascades, particularly for ACEIs and possibly statins. Pharmacists and clinicians should remain vigilant for ADRs at higher doses and consider dose reduction as a strategy to reverse or prevent prescribing cascades. Further research is necessary to assess the effectiveness of dose adjustments in preventing ADRs and prescribing cascades.

ORAL FOLINIC ACID PROPHYLAXIS PREVENTS PEMETREXED-INDUCED NEUTROPENIA: RESULTS FROM A RANDOMIZED CLINICAL TRIAL

R. Contrucci [ab]*, **R. ter Heine** [b], **M. Tonn** [a], **J Diepstraten** [a], **E van Thiel** [c], **C van Kesteren** [d], **M. van den Heuvel** [e], **C. van der Leest** [f] and **N. de Rouw** [ab]

[a] Department Clinical Pharmacy, Amphia Hospital, Breda.
[b] Department of Pharmacy, Radboud University Medical Center, Research Institute for Medical Innovation, Nijmegen.
[c] Department of Pulmonary Diseases, Albert Schweitzer Hospital, Dordrecht.
[d] Department Clinical Pharmacy, Albert Schweitzer Ziekenhuis, Dordrecht.
[e] Department of Pulmonary Diseases, Radboud University Medical Center, Nijmegen.
[f] Department of Pulmonary Diseases, Amphia Hospital, Breda.

* Correspondence: rcontrucci@amphia.nl.

Background

Pemetrexed is a cornerstone in the treatment of non-small cell lung cancer. Although this drug is generally well-tolerated, a substantial part of the patients receiving pemetrexed experience dose- or treatment-limiting toxicities, the foremost being neutropenia. Grade III/IV neutropenia has reported incidences up to 26% and can lead to hospitalization, treatment interruption, or even death. Based on in vitro and preclinical data pemetrexed-associated neutropenia can be prevented by treatment with prophylactic folinic acid.

Objective

The main objective of this study was to evaluate the effect of oral folinic acid in preventing pemetrexed-associated neutropenia.

Methods

A multicenter, open-label, double-arm, randomized trial was performed. Fifty patients treated with pemetrexed were randomized in a 1:1 ratio to either receive oral folinic acid 24 hours after pemetrexed administration for 3 days or receive standard of care without folinic acid. The primary endpoint was the difference in neutrophil count between both groups after the first cycle of chemotherapy at nadir. Secondary endpoints were the neutrophil count after the second cycle of chemotherapy, grade of neutropenia, efficacy of oncological treatment, renal function and the incidence of dose delays and reductions of pemetrexed.

Results

In total, 24 patients were included in the folinic acid group and 26 patients in the control group. Primarily, a higher absolute neutrophil count ($P < 0.01$) after the first cycle of chemotherapy was observed in the folinic acid group (median: 3.79; interquartile range [IQR]: 2.22-4.93) compared to the control group (median: 1.85; IQR: 1.43-3.78).
Secondarily, a higher neutrophil count ($P = 0.01$) was observed after the second cycle of chemotherapy in the folinic acid group (median: 2.60; IQR: 2.03-4.41) compared to the control group (median: 1.76; IQR: 0.87-2.73). The incidence of grade I neutropenia after the first cycle of chemotherapy was 4% in the folinic acid group vs. 27% in the control group ($P = 0.04$). The incidence of grade II neutropenia was 0% in the folinic acid group vs. 15% in the control group ($P = 0.05$). No differences were observed in the efficacy of treatment, renal function, dose reductions, delays, or discontinuation of treatment. Also no serious adverse events related to the treatment with folinic acid were observed.

Conclusions

Prophylaxis with oral folinic acid is effective in preventing pemetrexed-associated neutropenia and should be incorporated in the standard of care. Prospective evaluation after implementation may serve to validate our findings with respect to real-world reduction in toxicity and efficacy of lung cancer treatment.