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BENDAMUSTINE SHOWS LOW SWAIN-SCOTT S-CONSTANT, NUCLEOPHILIC SELECTIVITY, A BASIS FOR MARKED AND PROLONGED MYELOSUPPRESSION

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Statement of the Problem: Bendamustine HCl (BMH) is a bis-(2-chloroethyl) amine alkylating agent with a methyl-benzimadazole-butyric acid carrier moiety. BMH is used extensively in lymphoproliferative malignancies. No published data on its nitrobenzylpyridine (NBP) alkylating kinetics has been available and speculation exists about BMH's potential anti-purine mechanisms. The toxicity profile of severe myelosuppression from BMH is well known, but the prolonged hemogram nadirs are not well described.

Methodology & Theoretical Orientation: The 10-year single hematology-oncology practice (2006-2016) of CPS was reviewed for examples of BMH-related prolonged myelosuppression. Informed consent was obtained in seven screened patients. NBP reaction kinetics of BMH were studied by the Spears Method for Swain-Scott nucleophilic selectivity, s-constant determination using competing nucleophiles thiosulfate, thiocyanate, sulfite, phosphate, acetate and halide ions, sodium salts at pH 7 with triethylamine alkalinization.

Findings: Examples were identified of prolonged myelosuppression after BMH, e.g., neutropenia for 226 days in a 52-yr old woman with Stage IIIB Gr 1-2 follicular lymphoma after two cycles of BMH/rituximab therapy but with full recovery in CR. And a 60-yr old woman with Gr3 duodenal follicular lymphoma treated with six cycles of BMH/rituximab, who received subsequent R-CHOP for transformation to diffuse large B-cell lymphoma (DLBCL), who developed monosomy-7 MDS at two years and myelomonocytic leukemia at 5 years. Our chemical kinetic studies of BMH showed rapid nucleophilic substitution on NBP, approximately 2-3 times faster than for chlorambucil but much slower than for mechlorethamine. The Swain-Scott nucleophilic selectivity, or substrate s-constant of BMH, was 0.74, which is 0.2 units lower than classical ethyleneaimines, and is closer to reported s-values of nitrosourea and alkyl-sulfonate (e.g., busulfan) alkylating substrates. Low nucleophilic selectivity of BMH among weaker nucleophiles, and a narrower hydrolysis intercept were contributing findings to its low s-constant.

Conclusion & Significance: The low Swain-Scott s-constant of BMH may explain its toxicity profile of marked and prolonged myelosuppression, consonant with its increasing use as a myeloablative agent for bone marrow transplant conditioning.

Recent Publications

1. Spears C P (1981) Nucleophilic selectivity ratios of model and clinical alkylating agents by 4-(4'-nitrobenzyl) pyridine competition. Molecular Pharmacology 19:496-504.
2. Spears C P, Kang S I, Kundu N G, Shamma T and Olah G A (1997) Swain-Scott constants and alkylating agent drug design. Current Topics Medicinal Chemistry 2:85-100.
3. Barbin A, Bereziat J C, Croisy A, O'Neill I K and Bartsch H (1990) Nucleophilic selectivity and reaction kinetics of chloroethylene oxide assessed by the 4-(p-nitrobenzyl)pyridine assay and proton magnetic resonance spectroscopy. Chemico-Biological Interactions 73(2-3):261-277.

Biography

Colin Paul Spears, MD is a Medical Oncologist-Hematologist with a background in alkylating agent kinetics in collaboration with the late Prof. George Olah (Nobelist 1994, Chemistry) at the University of Southern California, where he pioneered nucleophilic selectivity assays. He was the first to study cancer drug target tumor biochemical effects, thymidylate synthase kinetics of fluoropyrimidine/folate enzyme inhibition with Prof. Charles Heidelberger. He is cited for the generalized fibonacci numbers, in discrete mathematics of asymmetric cell division work with Marjorie Bicknell-Johnson. He was a Chair of the Cancer Center at Mercy General Hospital in Sacramento, California for 10 years, in private practice from 2006-2016. He is a Professor of Hematology at California Northstate University College of Medicine, Sacramento, California.

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