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MSHP 2010 Practitioner Grant Recipient

Dosing of Busulfan in Overweight and Obese Patients Compared to Normal Weight Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Victoria Brown, PharmD, PGY-2 Oncology Resident - Principal Investigator
The Johns Hopkins Hospital

Co-investigators

1. Lindsey Lombardi, PharmD, Clinical Specialist, Bone Marrow Transplant
2. Amy Seung, PharmD, BCOP, Clinical Specialist, Hematologic Malignancies
3. Samantha Price, PharmD, Clinical Specialist, Hematologic Malignancies and Bone Marrow Transplant
4. Leo Luznik, MD, Associate Professor, Hematologic Malignancies

All co-investigators practice at The Johns Hopkins Hospital

Organization at which project will be conducted

The Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins Hospital

Primary Objective

To characterize busulfan area under the plasma concentration-versus-time curve (AUC) by body-mass index (BMI) classifications

- a. To determine the median number of dose adjustments necessary to achieve a busulfan AUC of 800 – 1400 $\mu\text{Mol}\cdot\text{min}/\text{L}$ for overweight and obese patients overall and within WHO classes of obesity I to III
- b. To determine the percentage of patients who achieve a busulfan AUC of 800 – 1400 $\mu\text{Mol}\cdot\text{min}/\text{L}$ at the first assessment for overweight and obese patients overall and within WHO obese classes I to III

Secondary Objectives

1. To compare busulfan AUC between overweight/obese and normal weight patients
 - a. To compare the median number of dose adjustments necessary to achieve a busulfan AUC of 800 – 1400 $\mu\text{Mol}\cdot\text{min}/\text{L}$ between overweight/obese and normal weight patients
 - b. To compare the percentage of overweight/obese and normal weight patients who achieve a busulfan AUC of 800 – 1400 $\mu\text{Mol}\cdot\text{min}/\text{L}$ at the first assessment
2. To compare the differences in clinical outcomes for overweight/obese and normal weights patients who receive busulfan as part of their preparative regimen
 - a. To compare overall survival between overweight/obese and normal weight patients

- b. To compare event-free survival between overweight/obese and normal weight patients
- c. To compare transplant-related mortality between overweight/obese and normal weight patients
- d. To compare the time to relapse between overweight/obese and normal weight patients

Background

Busulfan is commonly used as part of the preparative regimens for allogeneic or autologous hematopoietic stem cell transplants due to its toxicity to the bone marrow. The use of busulfan and cyclophosphamide as a preparative regimen was originally developed at The Johns Hopkins Hospital (JHH) in the 1970s. Busulfan is an alkylating agent which is toxic to hematopoietic stems cells with little effect on the lymphoid tissues. The reverse is true for cyclophosphamide. The regimen has been used with success at JHH.

The pharmacokinetic (PK) profile of busulfan has been shown to be related to a number of variables. Busulfan pharmacokinetics can be described via a one-compartment model in which elimination occurs in a single straight-line on a log-linear scale. Busulfan is metabolized via the glutathione S-transferase (GST) enzyme system in the liver. Hence, some have hypothesized that alterations in liver size and function along with genetic differences may influence this pathway. Busulfan has the ability to penetrate the central nervous system and is therefore associated with convulsions. Due to this association, patients are placed on seizure prophylaxis. At JHH, all patients are placed on phenytoin which is a known inducer of GST. Consequently, patients may experience a decrease in busulfan AUC secondary to an increase in GST metabolism.

Busulfan is known to have a narrow therapeutic index. Elevated area under the plasma concentration-versus-time curve (AUC) has been shown to be associated with increased risk of regimen-related toxicities including hepatic veno-occlusive disorder (VOD). However, low busulfan AUCs are correlated to increased risk of graft-rejection and disease relapse. A therapeutic range for AUC of 950 to 1500 $\mu\text{Mol}\cdot\text{min}/\text{L}$ has been reported to achieve the good clinical outcomes in a single-center study. The current range used at JHH is 800

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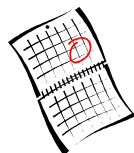
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**MARK YOUR CALENDARS
MSHP 2011 Activity Calendar**

The MSHP Board and Committee Chairs have put together the initial 2011 MSHP calendars of events and activities planned for the year. Please take a note of dates for this year's Bi-Annual Seminar, CE programs, newsletter deadlines and other items that may be of interest to you and your pharmacy colleagues. As details for these events will be announced in future *MSHP Pharmascript* issues or by e-mail.

February	
17th	Pharmacy Legislative Day State House-Annapolis
25th	Deadline to Submit Applications for Maryland Board of Pharmacy Acute Care Seat
March	
4th	Deadline to submit Spring Award Nominations: • Patient Safety • Technician of the Year
11th	Submission deadline for March/April MSHP newsletter.
26th	BiAnnual Seminar - Spring Maritime Institute- BWI
April	
16th	Wine Tasting Event University of Maryland - Student Center
May	
6th	Health Village at Baltimore Flower Mart Mount Vernon
13th	Submission Deadline for May/June MSHP Newsletter
18th	Eastern States Residency Conference Hershey, Pennsylvania
20th	University of Maryland School of Pharmacy Graduation - Presentation of MSHP Student of the Year Award
24th	MSHP Evening Post-Poster Presentation
June	
12-15	ASHP Summer Meeting Denver, Colorado
July	
8th	Submission deadline for July/August MSHP Newsletter.
27th	Director of Pharmacy Leadership Breakfast
August	
2nd	Evening CE program welcoming new area Residents

September	
9th	Submission deadline for September/October MSHP newsletter
22nd	Evening CE program Medication Errors
October	
18th	Residency Showcase University of Maryland School of Pharmacy
November	
4th	Deadline for Fall Award Nominations including: • Pharmacist of the Year • Jeffery Ensor Emerging Leadership Award • Industry Representative of the Year Award • Arthur W. Purdum Award
11th	Submission Deadline for November/ December MSHP Newsletter
December	
4-6	ASHP Midyear Meeting New Orleans, Louisiana
Programming planned by Other Area Pharmacy Organizations	
April	
16	Maryland Chapter—American Society of Consultant Pharmacists Spring Spectacular CE Program Linthicum Heights, Maryland
June	
12 –16	Maryland Pharmacists Association Annual Convention Ocean City, Maryland
August	
5-6	Maryland Chapter—American Society of Consultant Pharmacists Mid Atlantic Conference Annapolis, Maryland

– 1400 $\mu\text{Mol-min/L}$. However, recent work at JHH has revealed that a tighter range of 800 – 1000 $\mu\text{Mol-min/L}$ is associated with improved overall survival, event-free survival, transplant-related mortality, and relapse (verbal communication by L. Lombardi; abstract submitted). AUC is known to be directly proportional to oral clearance (CL/F) and directly proportional to dose.

There are two preparations of busulfan currently available on the market – intravenous and oral tablets. The usual starting doses are 1 mg/kg every 6 hours for the oral formulation and 0.8 mg/kg every 6 hours for the intravenous formulation. Due to population variation, these dosing schemes have been shown at to achieve a similar percentage of patients within the range of 800 – 1000 $\mu\text{Mol-min/L}$. By normalizing the dose to body size, variability in clearance amongst patients is reduced. However, the problem faced in dosing overweight or obese patients is the selection of an appropriate measure of body size for dose normalization. The use of actual body weight (ABW) is intuitively questioned.

The first study to elevate the impact of obesity elevated the apparent oral clearance (CL/F) in relation to body size in 279 adolescent and adult patients. This showed that significant determinants of CL/F were actual body weight, body surface area, 25% adjusted body weight, and ideal body weight. However, body mass index (BMI), height, age, gender, and disease were less important predictors. Notably the CL/F of obese patients (BMI 27-35 kg/m²) and severely obese patients (BMI >35 kg/m²) was found to be 17 and 32% higher than those with a normal BMI of 18-27 kg/m². This difference was not eliminated by expressing CL/F in terms of actual or ideal body weight. However, when expressed in terms relative to body surface area or adjusted body weight, CL/F was similar between normal and obese patients. Disease specific differences in CL/F between Non-Hodgkin's lymphoma patients and chronic myelogenous leukemia were also noted. Hence, the authors concluded that adjusting for body size would not serve to completely eliminate inter-patient variability.

A retrospective pharmacokinetic analysis of 127 adult patients who received 0.8 mg/kg IV busulfan every six hours for four days was undertaken to determine the parameters which were predictive of busulfan pharmacokinetics. Only body size parameters were able to explain the inter-patient variability. Body-surface area (BSA) and 25% adjusted body weight were the best determinants to explain inter-patient variability for both normal weight and obese patients whereas significant differences existed when based on actual or ideal body weight. The use of ABW in obese patients would have resulted in plasma over-exposure (44% of the AUCs from 1500 $\mu\text{Mol-min/L}$ to 2173 $\mu\text{Mol-min/L}$) while the use of IBW would have resulted in plasma under-exposure (17% of AUCs from 536 $\mu\text{Mol-min/L}$ to 900 $\mu\text{Mol-min/L}$). A fixed dose of 0.80 mg/kg based on adjusted body weight and 29 mg/m² of BSA yield an average AUC of 1200 $\mu\text{Mol-min/L}$, 80% of the patients within the author's predefined therapeutic range of 900 – 1500 $\mu\text{Mol-min/L}$.

Most recently, a retrospective review of 28 patients evaluated the effect of using adjusted versus actual body weight for initial

dosing of busulfan. The exact calculation used for adjusted body weight was not defined in this abstract. Patients were dosed using adjusted body weight if their actual body weight exceeded their ideal body weight by greater than 30%. Sixty-one percent of the patients (17/28) required a dose increased secondary to an AUC <900 $\mu\text{Mol-min/L}$. Of these patients requiring a dose increase 59% (10/17) were significantly overweight with a range of 31-112% over ideal body weight. The current adult practice at JHH is to dose busulfan based on the patient's ideal body weight (IBW). The one exception is for patients whose actual body weight is less than their ideal body weight, in which case actual body weight is used. Seven-point kinetics and six-point kinetics are used for oral and intravenous busulfan, respectively. These blood draws are then sent to an outside lab for processing. The results are forwarded to JHH Pharmacy Clinical Specialists to allow for dose adjustment. Anecdotal reports indicate the number of obese or severely obese patients undergoing bone marrow transplant has increased in the recent past. Optimization of first dose busulfan AUC leads to improved clinical outcomes. Therefore, characterization of the current practice is necessary to determine if this optimization is occurring in the obese patient population. Additionally, therapeutic dose monitoring will be more efficient if the initial dosing is as accurate as possible. The need for evaluation of the current busulfan dosing strategy is paramount

Methods: Study Design

- A retrospective chart review will include allogeneic HSCT adult patients admitted to the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins from 1/1/2004 to 7/31/2010 whose preparative regimen included busulfan and in whom at least busulfan AUC was calculated.
- This study will retrospectively compare busulfan dose adjustments and first busulfan AUC assessment between patients meeting World Health Organization (WHO) criteria for obesity to patients of normal body weight.
- The patients will consist of allogeneic HSCT adult patients whose preparative regimen included busulfan.
- The variable of interest is obesity as defined by the WHO.
- The primary outcomes of interest are number of dose adjustments necessary to achieve a busulfan AUC of 800 – 1400 $\mu\text{Mol-min/L}$ for overweight/obese patients overall and within WHO classes of obesity I to III and achievement of an AUC of 800 – 1400 $\mu\text{Mol-min/L}$ at the first assessment.
- A secondary outcome of interest is the median number of dose adjustments and percentage of patients who achieve a busulfan AUC of 800 – 1400 $\mu\text{Mol-min/L}$ at the first assessment for overweight/obese and normal weight patients.
- A secondary outcome of interest is to compare the following clinical outcomes: overall survival, event-free survival, transplant-related mortality and time to relapse between patients meeting WHO criteria for overweight/obesity to patients of normal body weight.
- The anticipated sample size is approximately 150 patients.

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- Data will be collected a data collection form and all patient identifiers will be de-identified.

Inclusion Criteria:

Adult HSCT recipients admitted to JHH from 1/1/2004 to 7/31/2010 whose preparative regimen included busulfan and had at calculated busulfan AUC.

Exclusion Criteria:

Patients enrolled in J0844

Data Collection:

Patient Identification:

Consecutive patients from 1/1/2004 to 7/31/2010 will be identified through a transplant database.

All patients meeting inclusion and exclusion criteria will be assessed. Once identified, patients will be evaluated for the presence of the outcomes of interest.

Patient Demographics:

Patient information will be collected through Electronic Patient Record database (EPR), Computerized Prescriber Order Entry (CPOE), Eclypsis, paper medical records and transplant clinical outcomes database.

Definitions:

- Ideal body weight (IBW) based on the Devine equations:
 - IBW (men): 50 kg + 2.3 kg/each inch over 5 feet
 - IBW (women): 45.5 kg + 2.3kg/each inch over 5 feet
- Adjusted Body Weight by 25% (AdjBW25): IBW + 0.25 (ABW – IBW)
- Adjusted Body Weight by 40% (AdjBW40): IBW + 0.40 (ABW – IBW)
- Body Mass Index (BMI): Actual body weight / (height²)
- BMI Classifications per WHO:¹⁰

Classification	BMI (kg/m ²)
Underweight	< 18.5
Normal range	18.5 – 24.99
Pre-obese	25 – 29.99
Obese class I	30 – 34.99
Obese class II	35 – 39.99
Obese class III	≥ 40

- Combinations of BMI classifications for purposes of secondary outcome comparisons:

Grouping Variable	BMI (kg/m ²)	WHO Classifications
Normal	< 25	Underweight Normal range
Overweight/Obese	≥ 25	Pre-obese Obese class I Obese class II Obese class III

- Overall survival: Time to death from any cause
- Event-free survival: Time to induction failure, relapse at any site, secondary malignancy or death
- Transplant-related mortality: Time to death secondary to transplant-related events including graft-versus-host disease, veno-occlusive disorder, graft-rejection and relapse
- Time to relapse: Time to relapse at any time of primary disease

Analytical plan:

- Demographics:** Descriptive statistics will be used to describe the baseline demographics of the BMI classification groups.
- Primary objective (Pharmacokinetic outcomes):** The primary objective will be characterized using the following descriptive statistics:
 - The median number of dose adjustments necessary to achieve a busulfan AUC of 800 – 1400 μMol-min/L for overweight/obese patients overall and within WHO classes of obesity I to III.
 - The percentage of patients who achieve a busulfan AUC of 800 – 1400 μMol-min/L at the first assessment for overweight/obese patients overall and within obese classes I to III.
- Secondary objective (Pharmacokinetic outcomes - Comparison):**
 - The grouping variable (normal or overweight/obese) will be the independent variable.
 - The outcome of interest are those listed below and will be the dependent variable:
 - Outcome #2A: Median number of dose adjustments necessary to achieve a busulfan AUC of 800 – 1400 μMol-min/L
 - Outcome #2B: Percentage of patients achieving a busulfan AUC of 800 – 1400 μMol-min/L with the first assessment
 - Null hypothesis (2a): The median number of dosing adjustments necessary to achieve a busulfan AUC of 800 – 1400 μMol-min/L will be the same between normal weight and overweight/obese patients.
 - The number of dosing adjustments for normal weight and overweight/obese patients are expected to be nonparametric. Therefore, the Wilcoxon rank-sum test will be used to determine if the medians of the normal weight and obese patients are different.
 - Null hypothesis (2b): The proportion of patients achieving a

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busulfan AUC of 800 – 1400 $\mu\text{Mol}\cdot\text{min}/\text{L}$ with the first assessment is same for normal weight and overweight/obese patients.

- The chi-square will be used to compare the proportion of patients achieving a busulfan AUC of 800 – 1400 $\mu\text{Mol}\cdot\text{min}/\text{L}$ with the first dose of busulfan between normal weight and overweight/obese patients.
- **Secondary objectives (Clinical outcomes - Comparison):**
- The grouping variable (normal or obese) will be the independent variable.
- The outcome of interest are those listed below and will be the dependent variable:
 - Overall survival
 - Event-free survival
 - Transplant-related mortality
 - Time to relapse

Null hypothesis: There is no difference in the frequency of the above clinical outcomes between normal weight and obese patients.

- A Kaplan-Meier product limit curve will be calculated for each BMI classification for all the above clinical outcomes. This will be done by calculating the cumulative survival at each time point that an event occurs.
- The Kaplan-Meier survival curves for each of the above clinical outcomes will be compared. The comparator group will be the patients with normal weight. The overweight/obese patients will be compared with the normal patient patients using the Mantel-Haenszel Chi-Square statistic and odds ratio calculation. This test will be preferred over the logrank test as the distribution of outcomes is unlikely to remain constant over time.

This project is inline with one or more of the American Society of Health System Pharmacy 2015 Initiatives

This project will help achieve two objectives under Goal 3 of 2015 Initiative (Goal 3: Increase the extent to which health-system pharmacists actively apply evidence-based methods to the improvement of medication therapy).

Objective 3.1 states that pharmacists will be actively involved in providing care to individual patients that is based on evidence, such as the use of quality drug information resources, published clinical studies or guidelines and expert consensus advice. The ultimate purpose of this project to add the body of literature related to dosing of busulfan in obese patients. As such, the results of this project will then be applied to our patient population at The Sidney Kimmel Comprehensive Cancer Center (SKCCC). As the pharmacy clinical specialists are currently managing dose adjustments of busulfan, this project will provide additional evidence on which to base their current practice. Furthermore, the data generated will

be presented at the Hematology/Oncology Pharmacy Association Meeting in March 2011. By sharing this data, pharmacists at other institutions will have evidence on which to based their practice with busulfan.

Objective 3.2 states pharmacists will be actively involved in the development and implementation of evidence-based drug therapy protocols and/or order sets. The evidence generated by this project will be used to further develop the drug therapy protocols and order sets for busulfan at SKCCC. The ultimate goal will be to develop a protocol and dosing plan which achieves the best pharmacokinetic and clinical outcomes for our obese patient population.

References

1. Santos GW, Tutschka PJ, Brookmeyer R, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. *N Engl J Med.* 1983; 309:1347-1353.
2. Russel JA, Kangaroo SB. Therapeutic drug monitoring of busulfan in transplantation. *Current Pharmaceutical Design.* 2008;14:1936-1949.
3. Grochow LB, Jones RJ, Brundrett RB, et al. Pharmacokinetics of busulfan: correlation with veno-occlusive disease in patients undergoing bone marrow transplantation. *Cancer Chemother Pharmacol.* 1989;25:55-61.
4. Andersson BS, Thall PF, Madden T, et al. Busulfan systemic exposure relative to regimen-related toxicity and acute graft-versus-host disease: defining a therapeutic window for IV BuCy2 in chronic myelogenous leukemia. *Bio Blood Marrow Transplant.* 2002;8:477-485.
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7. Nguyen L, Leger F, Lennon S, et al. Intravenous busulfan in adults prior to hematopoietic stem cell transplantation: a population pharmacokinetic study. *Cancer Chemother Pharmacol.* 2006;57:191-198.
8. O'Neal NK, DuBois LK, Williams CB, et al. Evaluation of the initial dose calculation of intravenous busulfan in adults receiving a conventional Bu/Cy2 allogeneic preparative regimen. *Bio Blood Marrow Transplant.* 2010;16:Abstract 96.
9. Devine BJ. Gentamicin therapy. *Drug Intell Clin Pharm* 1974;8:650-5.
10. BMI Classification. World Health Organization. © 2006. Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (accessed 8/20/10).

Proceeds from this grant will be used to defer expenses to present at the Hematology Oncology Pharmacists Association (HOPA) Annual Conference being held March 2011 in Salt Lake City, UT



Maryland Society of Health Systems Pharmacists ALL-DAY CE SEMINAR - Spring Session
FILTERING FACTS: FRAMEWORK FOR THE FUTURE

Saturday, March 26, 2011

Conference Center at the Maritime Institute

7:00 am - 8:25 am

Registration, Continental Breakfast & Exhibitor Visits

7:00 - 8:00 am - Directors of Pharmacy Leadership Breakfast

8:30 am -9:20 am

Dialysis Part 1 - Various Dialysis Methods

& When To Use What

Ron Abrahams, RPh

Hartford Hospital, University of Connecticut School of Pharmacy

AND

9:20 - 10:30 am

Dialysis Part 2 - Complications of CKD/ESRD

Continued with Dr. Abrahams

2.0 contact hours / 0.2 CEU's

10:30 - 11:00 am Break with Corporate Sponsors

11:00—12:00 noon

Health Care Reform

Anne

Powell

Healthcare Policy & Advocacy, Johnson & Johnson

1.0 contact hour / 0.1 CEU

12:00 - 1:00 pm

Luncheon & Spring Awards Presentation

(Technician & Patient Safety)

1:15 - 2:15 pm

Hyponatremia and the "Vaptans"

John Lindsley, PharmD, BCPS

The Johns Hopkins Hospital

1.0 contact hour/ 0.1 CEU

2:15 - 3:15 pm

MDRD vs. Cockcroft Gault

Thomas Dowling, PharmD

University of Maryland School of Pharmacy

1.0 contact hour/ 0.1 CEU

3:15 - 4:15 pm

Therapeutic Drug Monitoring in the CKD/ARF Patient

John J. Lewin PharmD, BCPS

The Johns Hopkins Hospital

1.0 contact hour/ 0.1 CEU

TECHNICIAN PROGRAMMING TO INCLUDE:

- Basic Dialysis Facts
- New Drug Update

Speakers to be announced

Schedule as of 01/28/2011. Updates to appear on website.

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**Please join us for
MSHP Wine Colloquium**

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**Wine Tasting and
hors d'oeuvres**

A fund raising event for MSHP
with our own wine aficionado

**Dr. John DiBona,
Director of Pharmacy - Sinai Hospital**

**Saturday April 16, 2011
6:30 pm**

At the new
University of Maryland Student Center
621 W. Lombard Street
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**Tickets are: \$50 per person
\$85 per couple**

To RSVP call or E-mail MSHP at
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The SMC Campus Center is located between the
HS/HS Library and the School of
Nursing.

Parking is available in the Penn
or Pratt garages. Access to the
garages is off of Pratt Street.
Street parking is also available.



**Bisphosphonates and Esophageal Cancer:
Sifting Through Conflicting Data**

Stacy Elder, PharmD

PGY-1 Pharmacotherapy Resident
The Johns Hopkins Hospital

Since their introduction, bisphosphonates have progressively been proven efficacious in the treatment of a variety of disease states resulting in bone resorption. Bisphosphonates act to reduce bone resorption by inhibiting osteoclasts. Widespread use of this medication class for treatment and prevention of osteoporosis, particularly in postmenopausal women, has become typical.¹ In post-menopausal women, bisphosphonates increased bone mineral density and decreased hip and vertebral fractures in clinical trials.^{2,3} Both enteral and intravenous bisphosphonate formulations exist, allowing for a wide degree of variability in dosing potency, schedule and indication for bone resorptive disorders.¹ Data has displayed the benefits of bisphosphonates in osteoporosis, increasing their prevalence in the drug regimens of the maturing population.¹ Due to their popularity, bisphosphonates have undergone public scrutiny for a variety of post-marketing adverse events, most recently, esophageal cancer.

Oral bisphosphonates can cause esophagitis, particularly when the patient does not take the medication before any food for the day, drink a full eight ounces of water and remain upright for 30 minutes after administration. The most recent concern has been the hypothesis that esophagitis related to bisphosphonates could indicate an increased risk of developing esophageal cancer. This concern was presented after the Food and Drug Administration (FDA) reported 23 cases and Europe and Japan reported 31 cases of esophageal cancer in patients using oral bisphosphonates. In response to this report, a retrospective cohort study was performed with the UK General Practice Research Database.⁴ Patients who were at least 40 years old with a prescription for oral bisphosphonates were paired with a control patient of the same age, gender, and general practice regardless of bisphosphonate use (to allow for treatment of cancer-related osteoporosis). Patients were excluded from the bisphosphonate group if they had a diagnosis of cancer within 3 years prior to initiation date, in order to get a clearer picture of whether patients developed cancer in actual relation to bisphosphonate use. After analyzing data for 46,036 patients in each cohort, 92 cases of esophageal were diagnosed in the control cohort and 89 cases in the bisphosphonate group, showing no difference in rate of esophageal cancer between patients on bisphosphonates and those who were not. Gastric cancer (to account for tumors at gastroesophageal junction) occurred in 57 patients in the control group and 49 patients in the bisphosphonate group. After adjustments for potential confounders, no difference was found in gastric/esophageal cancer between the bisphosphonate and control groups.⁴ While it is important to consider the limitations of a retrospective trial, this study lends the first evidence that bisphosphonates are not associated with increased risk of gastric or esophageal cancer with bisphosphonates.

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About a month after the publication of the first case-control study from the UK General Practice Research Database, another trial, gathering patient information from the same database, was published.⁵ This study matched patients with known esophageal, stomach and colorectal cancer to patients without cancer (1:5) and exposure to bisphosphonates was determined in these patients. A total of 2954 esophageal cancer cases were compared to 14,721 control cases and observed for an average of 7.5 years. In contrast to the previous study, patients with any exposure to bisphosphonates, defined as at least one prescription in the database, were found to have a significantly higher incidence of esophageal cancer (RR=1.30). Patients with greater than ten prescriptions for bisphosphonates had almost a two-fold higher risk of esophageal cancer (RR=1.93), and longer duration of exposure (>3 years, vs <1 year) was associated with an increased incidence. These results did not vary across stratified groups, including those who smoked, drank alcohol, were overweight, had prior gastrointestinal disease, or were on steroids, non-steroidal anti-inflammatory drugs or acid suppressants. This trial had a high number of esophageal cancer cases, as this was the method for choosing that arm of the study, with bisphosphonate prescription being the event of interest in each arm. The number of pertinent patients provided the ability to look at multiple patterns in cancer development, however, this trial is limited to records of prescriptions and ICD-9 codes of esophageal cancer, rather than separate investigators evaluating compliance with medication and legitimate diagnosis of esophageal cancer.⁵

The conflicting nature of these database reviews makes it difficult to assess the clinical implications of the information gathered. However, it is important to note that observation for the first trial was shorter and only patients with greater than 1095 daily bisphosphonate doses were included, possibly decreasing the ability to analyze a large sample size of patients and multiple patterns of cancer occurrence. ⁴ The second trial could more

accurately identify cancer incidence due to the design of information accrual, possibly making it more likely to detect a difference between exposure and non-exposure to bisphosphonates than the first trial. The utilization of bisphosphonates in western medicine is high, particularly in post-menopausal women, and those at risk for osteoporosis-related fracture. Though conflicting, the data from these two studies will likely be both conversation- and hypothesis-generating in the setting of high bisphosphonate use.

Pardon Our Disruptions During Construction



MSHP is currently with the Software Consortium to update and enhance our website making it more user friendly. When complete members will be able to:

Sign on to the member area to change their contact information, register for programs, volunteer for committees or take care of their annual dues. As time goes by we are looking to provide member updates and educational programs through webinar presentations.

To complete this update, there may be times our website is out of service. We apologize in advance for any inconveniences due to the disruptions.

Look for additional information on this update as well as an announcement of the official unveiling of the website in the next issue of the **MSHP Pharmascript**.



Thank you for your understanding.

Maryland Society of Health System Pharmacists
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