8-2016

Potentially Inappropriate Medication Use in Older Patient with Breast and Colorectal Cancer

Meghan S. Karuturi

POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER PATIENTS WITH BREAST AND COLORECTAL CANCER

by

Meghan Karuturi, MD

APPROVED:

Sharon H. Giordano, MD, MPH
Advisory Professor

Holly M. Holmes, MD, M.Sc.

Carlos H. Barcenas, MD, M.Sc.

Scott B. Cantor, Ph.D.

Gary E. Gallick, MS, Ph.D.

Robert C. Bast Jr, MD

POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER PATIENTS WITH BREAST AND COLORECTAL CANCER

A

THESIS

Presented to the Faculty of
The University of Texas
Health Science Center at Houston
and
The University of Texas
MD Anderson Cancer Center
Graduate School of Biomedical Sciences
in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF SCIENCE

by

Meghan Karuturi, MD
Houston, Texas

August, 2016

Dedication

This thesis is dedicated to my mentors, Drs. Holly Holmes and Sharon Giordano, and parents, Anila and Chaks Karuturi, who have supported me in different ways over the past years and made this possible.

Acknowledgements

This research was supported by the Duncan Family Institute and the American Society of Clinical Oncology (ASCO) 2014 Young Investigator Award.

POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER PATIENTS WITH BREAST AND COLORECTAL CANCER

Meghan Karuturi, MD

Advisory Professor: Sharon H. Giordano, MD, MPH

Our objective was to determine predictors of potentially inappropriate medication (PIM) use and its impact on outcomes (including ER visits, hospitalization, all cause death, and composite of three) in breast and colorectal cancer patients receiving chemotherapy. We used data from the SEER database linked to Medicare claims. Our cohort included patients ≥ 66 years diagnosed with of Stage II/III breast or colorectal cancer between 7/1/2007-12/31/2009. Baseline PIM was defined using the Drugs to Avoid in the Elderly list (DAE) or Beers criteria. Univariate and multivariable logistic regression were used to determine the associations of baseline PIMs with different covariates. Event-free survival (EFS) was defined from the initiation of chemotherapy to outcome, and estimated using the KM method. Cox proportional hazards modeling was used to determine the association of baseline PIMs with EFS. The final analysis included 1595 breast and 1528 colorectal patients. The frequency of baseline PIM was 22.2% (DAE) and 27.6% (Beers) in the breast cohort, and 15.5% (DAE) and 24.8% (Beers) in the colorectal cohort. Baseline PIM was associated with younger age, baseline ≥5 medications, and female gender. In the breast cohort, 37.5% patients had at least one composite outcome. One-year EFS rate was 49%, 62%, 96%, and 45% for ER, hospitalization, death, and composite respectively. Variables associated with increased risk of the composite outcome included baseline ≥5 medications, advanced stage, higher comorbidity, and baseline ER/hospitalization. Baseline PIM using

DAE was associated with increased risk of death in the breast cohort, HR 2.31 (95% CI 1.07-4.96). 45% of patients in the colorectal cohort had at least one composite outcome. One-year EFS rate was 42%, 54%, 91%, and 38% respectively. Variables associated with an increased risk of the composite outcome in colorectal patients included baseline ≥ 5 medications, older age, female gender, higher comorbidity. In the time-to-event analysis, we found no association between baseline PIM and most outcomes in either group, aside from baseline PIM using DAE and death in the breast cohort during chemotherapy. Baseline ≥ 5 medications was associated with increased risks of adverse outcomes in both. Our findings require further prospective confirmation but call into doubt the need to reduce PIM in older patients during chemotherapy.

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION

Polypharmacy and potentially inappropriate medication (PIM) use are highly prevalent in older patients with cancer, and are recognized as potential risk factors for adverse outcomes during cancer treatment.[1] Given the complexity of their diagnoses and presence of comorbidities, older adult patients with cancer are at high risk for PIM use.[2, 3] They not only receive medications that treat their comorbidity and malignancy, but also receive medications to treat therapy-induced toxicity (chemotherapy-induced nausea and vomiting, for example).[4-6] Furthermore, oncology patients are often seen by many different physicians, and subsequently prescribed several medications for overlapping indications.[7, 8] The National Comprehensive Cancer Network Guidelines for Senior Adult Oncology recommend review of medications and appropriate use at every visit, through screening tools validated in the general older adult population.[1]

PIMs are medications or classes of drugs that have been deemed to have a high risk-to-benefit ratio, and should thus be avoided in older persons.[9] The most commonly used measure of PIM is the Beers Criteria.[10] The Healthcare Effectiveness Data and Information Set (HEDIS) Drugs to Avoid in the Elderly (DAE) list is a subset of medications that are on the Beers list and represent medications that are high risk for adverse drug events.[11, 12] Both have been developed through expert consensus and are associated with adverse outcomes in the general older population. Amongst older adults, PIM use defined with the Beers criteria or DAE list is predictive of significant morbidity, more adverse drug events, increased emergency room visits, increased hospitalization and increased risk of mortality.[9,

13-15] However, there is a dearth of evidence suggesting that these tools are applicable to the older adult cancer population receiving chemotherapy.[1]

Studies have examined the patterns and impact of PIM in older cancer patients. In a cross-sectional study of 117 adults 65 and older with cancer, 41% were prescribed at least one PIM on the Beers criteria.[16] In a study published in 2015, Nightingale and colleagues demonstrated an incidence of PIM use defined by the 2012 Beers criteria, STOPP Criteria and Healthcare Effectiveness Data and Information Set (HEDIS) of 40%, 38% and 21% of patients respectively.[17] Maggiore et al demonstrated 29% PIM use based on the Beers Criteria.[3] An additional prospective observational study showed that polypharmacy and inappropriate medication use as defined by Beers were common and increased during hospitalization.[3] With the exception of the study by Maggiore et al, studies have not reported the impact of PIMs on adverse events while receiving chemotherapy. Maggiore and colleagues performed a secondary analysis of prospectively collected data of adults aged >/= 65 years to show that polypharmacy and PIM use, though common, were not associated with chemotherapy-related toxicity or hospitalization in older adults with cancer. However, this population was heterogeneous, composed of patients with several different cancer types and stages. The applicability of lists of PIMs to patients with advanced disease who would benefit from primarily palliative care is uncertain, as many drugs on the Beers list are also essential supportive care medications for end-of-life care. Studies are needed to determine whether such supportive care medications are actually harmful in patients receiving chemotherapy, and whether the risk/benefit profile truly favors discontinuation of PIMs. To evaluate the impact of PIM on clinical outcomes, we evaluated PIM use in a large population-based cohort of older adult cancer patients receiving chemotherapy, identified

through the SEER-Medicare database. We selected breast or colorectal cancer patients receiving adjuvant therapy, a group for whom there might be a reasonable assumption that chemotherapy was intended to be curative. The two metrics of PIM use we applied were the 2012 Beer's Criteria and HEDIS list. Our objective was to determine the presence of predictive factors for baseline PIM use and the impact of baseline PIM use on health outcomes during the course chemotherapy.

PATIENTS AND METHODS

Data Source

We used the merged SEER-Medicare database as our data source. The SEER database is a population-based tumor registry sponsored by the National Cancer Institute that contains information on all newly diagnosed cancer cases that occur in persons residing in SEER participating areas. The SEER database includes approximately 28% of the US population, and collects information on patient demographics, tumor characteristics, stage at diagnosis, date of diagnosis, treatment, and date/cause of death. Medicare claims data are linked with SEER and include outpatient, inpatient and physician claims.

Around 60% of Medicare beneficiaries have Part D coverage, a federal program to subsidize the cost of prescription drugs. Part D Prescription Drug Events (PDE) files include beneficiary identifiers that have been linked with Medicare claims files, and include drug name, fill date, National Drug Code (NDC) number, quantity dispensed, number of days' supply, cost and other plan-based variables.

Study Population

This study included individuals diagnosed between 7/1/07 and 12/31/09 with American Joint Committee on Cancer Modified third edition Stage II and III breast or colorectal cancer, age 66 years of older, who received chemotherapy within 6 months of diagnosis. Identified individuals were required to have Medicare Part A and B coverage starting a minimum of 12 months prior to diagnosis and 12 months following, and Part D coverage from 4 months prior to 12 months after diagnosis. Patients who were members of a

health maintenance organization for 1 year before and 1 year following diagnosis were excluded, due to incomplete claims. Men with breast cancer were excluded.

We used the Common Procedure Terminology J codes in the SEER-Medicare Outpatient, Physician/Supplier and Durable Medical Equipment files identify adjuvant chemotherapy use. To be considered adjuvant chemotherapy, claims had to begin within 6 months of diagnosis. The end date of active treatment was determined based on the appearance of final J-codes for chemotherapy administration, with no further treatment administered for at least a 90-day period. Chemotherapy regimens were also identified as combination or single-agent. For breast cancer, regimens were classified as an anthracycline-based regimen if J codes for doxorubicin, epirubucin, or mitoxantrone were present. For colorectal cancer, regimens were determined to be multi-agent if they contained oxaliplatin-based on J codes. Comorbid conditions present during 1 year prior to diagnosis of cancer were determined using the International Classification of Disease (ICD-9) diagnosis and procedure codes to search the Medicare inpatient, outpatient and physician claims data. Education and poverty are provided as a census tract-level variable, and identified as the percentage of patients with less than 12 years of education or those living below the poverty line based on zip code and census tract level.

Statistical Analysis

The first objective was to determine the prevalence and predictors of baseline PIM use in older adult patients with breast or colorectal cancer receiving chemotherapy in the adjuvant setting. PIM use was defined based on the Beers 2012 Criteria and Drugs to Avoid in the Elderly (DAE) list. Both tools have been used for retrospective application to administrative data.[11] The exposure period for detecting baseline PIMs ranged 4 months before diagnosis

up to the date of diagnosis, counting any medications that satisfied the definition of PIM as per the aforementioned criteria. Each of these tools resulted in a dichotomous measure of PIM (present or absent). PIM rates were also evaluated during the periods 0 to 3 months and 3 to 6 months after the initiation of chemotherapy.

Demographic variables included patient age (66-70, 71-75, 76-80, 80+), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), sex (for the colon cancer subgroup only), census tract-based education (in quartiles) and poverty (in quartiles) levels. Clinical variables included year of diagnosis (2007, 2008, 2009), stage (II, III), Charlson comorbidity index (0, 1, 2+), baseline number of medications (0-4, 5-10, 11+), baseline number of outpatient professional medical care providers (0-1, 2-3, 4+), and chemotherapy regimen (anthracycline-based and oxaliplatin-containing with the breast and colorectal cancer patients, respectively). Comorbidity score was calculated using Klabunde's adaptation of the Charlson comorbidity index from the macro provided by the National Cancer Institute.[18]

PIM rates and other baseline sample characteristics were summarized for each disease subgroup using descriptive statistics. Univariate and multivariable logistic regression were used to examine the association of study covariates with each PIM measure. Covariates associated with PIM at the 0.2 significance level were candidates for the multivariable model, and those variables with p-values of less than 0.05 were retained with application of a backward model selection. Statistically and clinically significant variables were retained in the final model, with results expressed as odds ratios (OR) and 95% confidence intervals (CIs).

A second objective of the study was to determine whether baseline PIM use in older adults receiving chemotherapy was predictive of poor clinical outcomes; emergency room (ER) visits, hospitalization, death, and the composite of three. We evaluated the two measures of PIM use (i.e., Beers and DAE) separately. Event-free survival was defined from the initiation of chemotherapy to outcome (event) or 3 months post chemotherapy. Patients were right-censored at the 3 months post last chemotherapy (defined as no further J-codes for chemotherapy within 90 days from the last J code). Hospitalization was defined as having one or more claims for a hospital stay, and was found in Medicare Provider Analysis and Review (MEDPAR) files. ER visits were defined as having one or more claims for an ER admission, derived from part B files. Finally, mortality was considered to be death from any cause. The same independent variables used in the analysis of baseline PIM were included in the univariate analysis.

One-year event free survival rates were calculated using the Kaplan-Meier product limit method with 95% confidence intervals (CI). Cox proportional hazards (PH) models were fitted to determine the association of patient and clinical characteristics with time-to-outcome endpoints. Variables retained in the final model were based on both statistical and clinical significance. Results were expressed in hazard ratios (HR) and 95% CIs. P-values less than 0.05 were considered to be significant, and all tests were two-sided. All statistical analyses were performed in SAS Version 9.3. (SAS Institute, Cary NC)

RESULTS

The final analysis included 1595 breast and 1528 colorectal cancer patients. Baseline characteristics are shown in Table 1. The frequency of baseline PIM by DAE and Beers criteria, respectively, were 22.2% and 27.6% in the breast cancer cohort, and 15.5% and 24.8%, respectively, in the colorectal cohort. Other than DAE in the breast cancer cohort, at a time interval of 0-3 months after initiation of chemotherapy, the frequency of PIM use in both cohorts using both measures increased (22% and 33.3% in the breast cancer cohort applying DAE and Beers respectively, and 20% and 28.9% in the colorectal cohort). In all cases, PIM use decreased at an interval 3-6 months following initiation of chemotherapy (11.2% and 18.1% in the breast cancer cohort applying DAE and Beers respectively, and 11.1% and 16.7% in the colorectal cohort; Table 2).

TABLE 1: Patient Characteristics

	Breast Cancer Cohort (N = 1595)	**Colorectal Cancer Cohort** (N = 1528)
Race		
White, non-Hispanic	1212(76.0%)	1127(73.8%)
Black, non-Hispanic	176(11.0%)	113(7.4%)
Hispanic	120(7.5%)	140(9.2%)
Other	87(5.5%)	148(9.7%)
Gender		
Male		758(49.6%)
Year of first diagnosis		
2007	319(20.0%)	318(20.8%)
2008	658(41.3%)	615(40.2%)
2009	618(38.7%)	595(38.9%)
Age at diagnosis		
66 - 70	712(44.6%)	563(36.8%)
71 - 75	497(31.2%)	442(28.9%)
76 - 80	240(15.0%)	348(22.8%)
>80	146(9.2%)	175(11.5%)
Stage		
II	1062(66.6%)	402(26.3%)
III	533(33.4%)	1126(73.7%)
Charlson comorbidity index		

	Breast Cancer Cohort	Colorectal Cancer Cohort
0	923(57.9%)	856(56.0%)
1	440(27.6%)	402(26.3%)
2+	232(14.5%)	270(17.7%)
Percent below the poverty level		
Lowest quartile	400(25.1%)	382(25.0%)
Second quartile	399(25.0%)	383(25.1%)
Third quartile	396(24.9%)	381(25.0%)
Highest quartile	398(25.0%)	381(25.0%)
Percent with a high school education (Breast cancer)		
Lowest quartile	399(25.0%)	382(25.0%)
Second quartile (24.08% - 30.84%)	400(25.1%)	383(25.1%)
Third quartile (30.84% - 37.25%)	396(24.9%)	381(25.0%)
Highest quartile (37.25% - 53.53%)	398(25%)	381(25.0%)
Number of care providers at baseline		
0-1	652(40.9%)	669(43.8%)
2-3	722(45.3%)	638(41.8%)
4+	221(13.9%)	221(14.5%)
Number of different medications at baseline		
0-4	420(26.3%)	440(28.8%)
5-10	667(41.8%)	627(41.0%)
11+	508(31.8%)	461(30.2%)
Chemo regimen (breast cancer)		
Anthracycline-based	493(30.9%)	
Non-Anthracycline-based	1102(69.1%)	
Chemo multi-regimen (colorectal cancer)		
No		670(43.8%)
Yes		858(56.2%)

TABLE 2: Frequency of PIM use during different time periods

		Breast Cancer Cohort	Colorectal Cancer Cohort
Measure	Period	Frequency	Frequency
DAE	Baseline	354/1595 (22.2%)	237/1528 (15.5%)
	Pre-Chemo	397/1595 (24.9%)	302/1528 (31.3%)
	0-3 mos	351/1595 (22.0%)	306/1528 (20.0%)
	3-6 mos	77/685 (11.2%)	84/759 (11.1%)
Beers	Baseline	440/1595 (27.6%)	379/1528 (24.8%)
	Pre-Chemo	545/1595 (34.2%)	478/1528 (31.3%)
	0-3 mos	531/1595 (33.3%)	442/1528 (28.9%)
	3-6 mos	124/685 (18.1%)	127/759 (16.7%)

In the univariate analysis, patient characteristics associated with baseline PIM use in the breast cancer cohort included higher level of comorbidity, number of care providers and number of different medications utilizing the both the DAE list and Beers. Baseline PIM use

as defined by DAE and Beers in the multivariable analysis was associated with the number of different medications and younger age. Among the colorectal cohort, patient characteristics associated with baseline PIM in the univariate analysis included number of different medication at baseline, higher comorbidity, and female gender utilizing both criteria. Additionally, baseline PIM defined by DAE was associated with a younger age group, and white race was associated with baseline PIM via Beers. In the multivariable analysis, PIM use applying either criterion was associated with female gender, and number of different medications (Table 3). Furthermore, there was an association with younger age and baseline PIM use in defined by DAE, and non-Hispanic white race using Beers

TABLE 3: Factors Associated w/Baseline PIM use (3A via DAE, 3B via Beers)

3A: DAE

	Breast Cancer Cohort		**Colorectal Cancer Cohort**	
Characteristic	Univariate OR (95% CI), p-value	Multivariable OR (95% CI), p-value	Univariate OR (95% CI), p-value	Multivariable OR (95% CI), p-value
Age at Diagnosis				
66-70	Ref		Ref	
71-75	0.89 (0.68-1.17)	0.83 (0.62-1.11), p=0.21	0.97 (0.69-1.35), p=0.84	0.86 (0.61-1.22), p=0.39
76-80	0.88 (0.62-1.24), p=0.46	0.79 (0.55-1.14), p=0.21	0.77 (0.53-1.12), p=0.17	0.66 (0.44-0.97), p=0.035
>80	0.56 (0.35-0.91), p=0.02	0.44 (0.27-0.72), p=0.001	0.55 (0.32-0.94), p=0.029	0.41 (0.24-0.71), p=0.0008
Gender				
Male	NA	NA	Ref	Ref
Female	NA	NA	1.71 (1.29-2.28), p=0.0002	1.66 (1.24-2.24), p=0.0008
Charlson Index				
0	Ref		Ref	
1	1.4 (1.07-1.84), p=0.014		1.9 (1.37-2.63), p= 0.0001	
2+	1.71 (1.23-2.38), p=0.001		2.54 (1.79-3.61), p= <0.0001	

	Breast Cancer Cohort		**Colorectal Cancer Cohort**	
# Care Providers				
0-1	Ref		Ref	
2-3	1.35 (1.04-1.76), p=0.023		1.11 (0.82-1.51), p=0.5	
4+	1.85 (1.3-2.62) p=0.0006		1.46 (0.98-2.17), p= 0.06	
# Different Medications				
0-4	Ref		Ref	
5-10	2.99 (1.99-4.5), p= <0.0001	3.14 (2.09-4.73), p<0.0001	3.81 (2.29-6.35), p= <0.0001	4.07 (2.41-6.87), <0.0001
11+	7.24 (4.84-10.84), p=<0.0001	7.67 (5.11-11.5), p=<0.0001	8.33 (5.04-13.78), p= <0.0001	8.84 (5.26-14.84), p<0.0001

*OR = odds ratio, CI = Confidence Interval, NA = Not Applicable, Ref = Reference case

3B: Beers

	Breast Cancer Cohort		**Colorectal Cancer Cohort**	
Characteristic	Univariate OR (95% CI), p-value	Multivariable OR (95% CI), p-value	Univariate OR (95% CI), p-value	Multivariable OR (95% CI), p-value
Age at Diagnosis				
66-70	1		1	
71-75	1.04 (0.8-1.34)	0.78	1.04 (0.78-1.38)	
76-80	0.85 (0.61-1.18)	0.33	0.88 (0.64-1.2)	
>80	0.8 (0.53-1.21)	0.29	1.04 (0.7-1.53)	
Race				
Non-Hispanic White	Ref		Ref	Ref
African American	0.95 (0.66-1.35)		0.67 (0.41-1.1)	0.6 (95% CI 0.36-1), p = 0.049
Hispanic	0.94 (0.62-1.44)		0.7 (0.45-1.09)	0.65 (0.41-1.04), p = 0.07
Other	0.99 (0.61-1.61)		1.28 (0.88-1.87)	1.13 (0.76-1.69), p = 0.55
Gender				
Male	NA	NA	Ref	Ref
Female	NA	NA	1.53 (1.21-1.93)	1.35 (1.05-1.73), p 0.02
Charlson Index				
0	Ref		Ref	
1	1.71 (1.33-2.21)		1.83 (1.39-2.41)	
2+	2.58 (1.9-3.5)		2.56 (1.89-3.46)	
Number of Care Providers				
0-1	Ref		Ref	
2-3	1.54 (1.2-1.96)		1.13 (0.87-1.46)	
4+	1.89 (95% 1.35-1.53)		1.94 (1.39-2.7)	
Number of Different Medications				
0-4	Ref	Ref	Ref	Ref
5-10	3.44 (2.36-5.01)	3,44 (2.36-5.01)	4.34 (2.85-6.6)	4.3 (2.82-6.55), p< 0.0001
11+	8.45 (5.8-12.31)	8.45 (5.8-12.31)	11.15 (7.33-16.96)	10.94 (7.18-16.68), p< 0.0001

*OR = odds ratio, CI = Confidence Interval, NA = Not Applicable, Ref = Reference case

In the time-to-event analysis (Table 4), the median follow-up for the breast cancer cohort was 5.7 months (0-9 months), with a one-year EFS rates of 49% (95% CI, 46%-52%), 62% (95% CI, 59%-65%), 96% (95% CI, 94%-97%), for the outcomes of ER visits, hospitalization, and death accordingly. The one-year EFS rate for the composite outcome of the three was 45% (95% CI, 42%-48%). For the breast cancer patients in the time frame of initiation of chemotherapy to 3 months post last chemotherapy, there were 42.9% patients

who had at least one ER visit. The multivariable analysis noted an association of increased risk of ER visits with older age, advanced stage, higher comorbidity, baseline 5 or more medications, and baseline ER visits. A total of 23.1% patients had hospitalization at least once, and an increased risk of hospitalization in the multivariable analysis was associated with Hispanic race, advanced stage, higher comorbidity score, and baseline 5 or more medications. A total of 2.1% patients died, and increased risks of death were associated with older age, advanced stage, and baseline PIM defined by the DAE list. Finally, a total of 37.5% patients experienced at least one of the three composite outcomes, and increased risks of ER / hospitalization / death were associated with advanced stage, higher comorbidity, baseline 5 or more medications, and baseline ER/hospitalization. Baseline PIM defined by DAE only associated with overall survival in in the time-to-event analysis, but there were not other associations between baseline PIM by either criteria with any other independent outcomes (Table 5).

TABLE 4: Summary for time (from first chemo)-to-event (ER, hospitalization, death, composite) for Breast and Colorectal Cohort

	ER	Hospitalization	Death	ER visits/ Hospitalization/ death
Breast cancer				
Number of event (%)	552 (34.6%)	369(23.1%)	34(2.1%)	598 (37.5%)
Median follow up (months)	5.0	5.1	5.7	5.0
Range follow up (months)	(0, 9)	(0, 9)	(0, 9)	(0, 9)
1-year event-free rate	0.49 (0.46,0.52)	0.62(0.59, 0.65)	0.96(0.94, 0.97)	0.45 (0.42, 0.48)
Colorectal cancer				
Number of event (%)	621(40.6%)	450(29.5%)	76(5.0%)	687 (45.0%)
Median follow up (months)	4.3	5.1	5.9	4.2
Range follow up (months)	(0, 9)	(0, 9)	(0, 9)	(0, 9)
1-year event-free rate	0.42 (0.39, 0.45)	0.54 (0.51, 0.58)	0.91(0.88, 0.92)	0.38(0.35, 0.41)

Table 5: Cox Proportional Hazards Model for time-to-event by Baseline PIM for Breast Cancer Cohort

PIM Measure	Time to 1st ER HR (95% CI, p-value)	Time to 1st Hospitalization HR (95% CI, p-value)	Overall Survival HR (95% CI, p-value)	Time to 1st ER/Hospitalization/Death HR (95% CI, p-value)
DAE	0.96 (0.78 to 1.18, p= 0.68	0.96 (0.75-1.23, p= 0.73)	2.31 (1.07-4.96, p= 0.033)	0.96 (0.79 to 1.17, p= 0.68)
Beer's	1.02 (0.85 to 1.24, p= 0.831)	1 (0.79 to 1.26, p= 1.0)	1.86 (0.88 to 3.96, p-0.11)	0.99 (0.82 to 1.19, p= 0.92)

In the colorectal cohort, the median follow-up was 5.9 months (0-9 months), with a one-year EFS rate of 42% (95% CI, 39%-45%) for ER visits, 54% (95% CI, 51%-58%) for hospitalization, 91% (95% CI, 88%-92%) for all cause death, and 38% (95% CI, 35%-41%) for the composite outcome. For the colorectal cancer cohort in the time frame defined, 40.6% of patients had at least one ER visit, and increased risks of ER visits were associated with older age, female gender, higher comorbidity, non-Hispanic white race, baseline 5 or more medications, and baseline ER visits. Hospitalization occurred in 29.5% of patients, and increased risks of hospitalization were associated with older age, female gender, non-Hispanic white race and higher comorbidity. Death occurred in 5%, and risks of death were associated with older age and higher comorbidity. Finally, 45% had a composite outcome, and increased risks of ER / hospitalization / death were associated with older age (76-80 vs 66-70), female gender, non-Hispanic white race, higher comorbidity, and baseline medications. Similar to the breast cancer cohort, there was no association of baseline PIM use according to the baseline PIM defined by both criteria and any outcome (Table 6).

Table 6: Cox Proportional Hazards Model for time-to-event by Baseline PIM for Colorectal Cohort

PIM Measure	Time to 1st ER visit HR (95% CI, p-value)	Time to 1st Hospitalization HR (95% CI, p-value)	Overall Survival HR (95% CI, p-value)	Time to 1st ER visit/Hospitalization/Death HR (95% CI, p-value)
DAE	0.99 (0.8 to 1.23, p= 0.94)	1.02 (0.79 to 1.32, p= 0.87)	0.8 (0.4 to 1.59, p = 0.53)	0.96 (0.78 to 1.19, p= 0.72)
Beers	0.96 (0.79 to 1.16, p = 0.65)	1.01 (0.81 to 1.27, p = 0.9)	0.8 (0.4 to 1.59, p = 0.53)	0.96 (0.78 to 1.19, p = 0.72)

DISCUSSION

In this study, we found that the frequency of PIM use in older patients with breast and colorectal cancer receiving chemotherapy in the curative setting ranged from 16% to 25% at baseline, depending on the criteria applied and the tumor type. Our study is unique in that it is the largest and only population-based study looking at PIM use in cancer patients receiving active treatment. Furthermore, it is the only study looking at PIM use in a relatively homogenous group of cancer patients receiving chemotherapy for curative intent. Our data are consistent with other studies that have evaluated the frequency of PIM use in an ambulatory older adult cancer patient population. Most recently, Nightingale et al conducted a retrospective study of pharmacist-led medication assessment in 248 adults with a mean age of 80, 87% of whom had solid tumors, and 16.3% with disease that was deemed advanced stage or metastatic.[17] In addition to capturing information on number of medications (where polypharmacy was defined as concurrent use of five or more medications and excessive polypharmacy as concurrent use of 10 or more medications), PIM use was categorized through the application of three screening tools that included the 2012 Beers criteria, the Screening Tool of Older Person's Prescriptions (STOPP) criteria, and HEDIS

DAE list. The mean number of mediations used was 9.23, with the prevalence of polypharmacy and excessive polypharmacy of 41% and 43% respectively. The frequency of PIM use was noted to be 40% utilizing Beer's criteria, 38% via STOPP, and 21% through DAE. The higher incidence of PIM use in this particular study is likely due to the fact that they were able to capture information on over-the counter medications, such a non-steroidal anti-inflammatory drugs (NSAIDs) and first-generation antihistamines, the absence of which is a limitation in the use of Medicare Part D data. In fact, both NSAIDs and first-generation antihistamines were amongst the most prevalent PIMs identified, at 8.5% and 6% respectively.

We did identify that certain patient and disease characteristics were associated with PIM use. In both cohorts, use of 5 or more medications at baseline was associated with PIM use in the multivariable analysis. Interestingly, a relatively younger age group of (less than 80 years old) was also associated with PIM use. Finally, in the colorectal cancer patients specifically, female gender was also associated with PIM use at baseline. The association of polypharmacy and PIM use has been corroborated in several publications. Nightingale and colleagues confirmed this in their study, as did Prithviraj in a publication from 2012.[16, 17] Prithviraj et al found that patients taking five or more medications concurrently were significantly more likely to be prescribed a PIM defined by the Beers 2012 criteria. The authors identified that these patients were also likely to have a poorer functional status or have 5 or greater comorbidities. Nightingale and colleagues similarly found a significant association between number comorbidities and ECOG performance stratus. Although this association between polypharmacy and comorbidity with baseline PIM use was seen in the univariate analysis, it was not a factor of significance in the multivariable analysis. A factor

unique to our analysis was the association of a relatively younger age group with higher rates of PIM use at baseline.

Finally, in the time-to-event analysis, we found that there was no association between PIM use at baseline and most adverse clinical outcomes that included ER visits, hospitalization or death during the course of chemotherapy. The only association of significance in the time-to-event analysis was baseline PIM defined by DAE and death in the breast cancer group. However, given the inconsistency of these findings, no firm conclusions can be made. Our findings confirm those published by Maggiore and colleagues in 2014.[3] The patient population in this study included 500 patients aged 65 and older (mean age 73 years), and a majority (61%) had metastatic disease secondary to a solid tumor. A vast amount of data was prospectively collected prior to start of systemic therapy, including a comprehensive geriatric assessment evaluating several functional and psychosocial domains in addition to a complete list of all medications the patient was currently taking (both prescription and non-prescription). Standardized approaches were applied to evaluate polypharmacy and PIM, and included the 2012 Beers criteria, Zhan criteria and 2011 DAE list. Outcomes of interest included grade 3-5 chemotherapy-related toxicity, and hospitalization during chemotherapy course. The authors found that there was no apparent association between the number of daily medications or PIM use defined by any of three criteria and toxicity or hospitalization use. They also looked at high-risk drug classes not considered PIMs that have been associated with adverse events (anticoagulants, antiplatelet, opioids, insulin, oral hypoglycemics and antiarrhythmic) and found no association with outcome. An advantage of Maggiore's study was that it was prospective, allowing the opportunity to capture a large amount of patient specific data. However, the authors

acknowledge that their evaluation of polypharmacy and PIM use was cross-sectional and performed in a secondary analysis, with limited data on certain components of medications use (such as dosage, frequency, indication, etc).

One major strength of our study was the inclusion of a large number of patients that were homogenous in regard to their disease stages and indication for treatment. However, the major limitation in our study was that it was retrospective, with the ability to include only a limited amount of data regarding patient and disease related characteristics as well as medications. Additionally, we only captured a cross-sectional assessment of PIM use. We did try to account for this by only considering medications for which there was a 90-day supply or multiple refills. However, it is entirely possible that these medications were not actively taken during the course of chemotherapy in our patients. Furthermore, Medicare Part D data does not include over-the-counter medications such as NSAIDs and antihistamines, which have been captured in previous studies as prevalent medication classes of PIM use.

These results suggest that PIM use alone at baseline is not definitively associated with poor clinical outcomes in cancer patients receiving systemic therapy. It is possible that patients did not actually continue to take PIMs once they were diagnosed with cancer and initiated chemotherapy. In addition, several supportive care medications that are considered PIMs may carry more benefit than harm for this select group of patients. Conversely, it may be that there are specific drugs or classes of PIM that carry the greatest risk, and should be looked at with greater scrutiny. In order to determine this, more prospective studies are required, that accurately capture PIM use and adherence to PIM agents in various patient and treatment settings (adjuvant, metastatic, etc). Baseline data in such studies should also

include components of the geriatric assessment, in order to best control for confounding factors related to comorbidity and frailty that may account for discrepant outcomes. However, our findings call into question the attention to which clinicians should invest to the screening of PIM use in our older adult cancer patient population receiving chemotherapy.

REFERENCES

1. Hurria A: Management of elderly patients with cancer. *J Natl Compr Canc Netw* 2013, 11(5 Suppl):698-701.
2. Hurria A, Wong FL, Villaluna D, Bhatia S, Chung CT, Mortimer J, Hurvitz S, Naeim A: Role of age and health in treatment recommendations for older adults with breast cancer: the perspective of oncologists and primary care providers. *J Clin Oncol* 2008, 26(33):5386-5392.
3. Maggiore RJ, Dale W, Gross CP, Feng T, Tew WP, Mohile SG, Owusu C, Klepin HD, Lichtman SM, Gajra A *et al*: Polypharmacy and potentially inappropriate medication use in older adults with cancer undergoing chemotherapy: effect on chemotherapy-related toxicity and hospitalization during treatment. *J Am Geriatr Soc* 2014, 62(8):1505-1512.
4. Voll ML, Yap KD, Terpstra WE, Crul M: Potential drug-drug interactions between anti-cancer agents and community pharmacy dispensed drugs. *Pharm World Sci* 2010, 32(5):575-580.
5. Chan A, Tan SH, Wong CM, Yap KY, Ko Y: Clinically significant drug-drug interactions between oral anticancer agents and nonanticancer agents: a Delphi survey of oncology pharmacists. *Clin Ther* 2009, 31 Pt 2:2379-2386.
6. Yap KY, Chui WK, Chan A, Onco-Informatics G: Development of a chemotherapy regimen interaction database for the mobile internet: detecting interactions with psychotropics through OncoRx-MI. *Inform Health Soc Care* 2011, 36(3):132-146.
7. Lichtman SM, Boparai MK: Anticancer drug therapy in the older cancer patient: pharmacology and polypharmacy. *Curr Treat Options Oncol* 2008, 9(2-3):191-203.
8. Tam-McDevitt J: Polypharmacy, aging, and cancer. *Oncology (Williston Park)* 2008, 22(9):1052-1055, discussion 1055, 1058, 1060.
9. Lund BC, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ: Inappropriate prescribing predicts adverse drug events in older adults. *Ann Pharmacother* 2010, 44(6):957-963.
10. By the American Geriatrics Society Beers Criteria Update Expert P: American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2015, 63(11):2227-2246.
11. American Geriatrics Society Beers Criteria Update Expert P: American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2012, 60(4):616-631.
12. (NCQA). NCfQA: Durgs to be Avoided in Elderly. HEDIS 2012.
13. Klarin I, Wimo A, Fastbom J: The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. *Drugs Aging* 2005, 22(1):69-82.
14. Hanlon JT, Maher RL, Lindblad CI, Ruby CM, Twersky J, Cohen HJ, Schmader KE: Comparison of methods for detecting potential adverse drug events in frail elderly inpatients and outpatients. *Am J Health Syst Pharm* 2001, 58(17):1622-1626.
15. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D: Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med* 2011, 171(11):1013-1019.
16. Prithviraj GK, Koroukian S, Margevicius S, Berger NA, Bagai R, Owusu C: Patient Characteristics Associated with Polypharmacy and Inappropriate Prescribing of Medications among Older Adults with Cancer. *J Geriatr Oncol* 2012, 3(3):228-237.
17. Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A: Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. *J Clin Oncol* 2015, 33(13):1453-1459.

18. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987, 40(5):373-383.

VITA

Meghan Karuturi was born in Rochester, New York on November 12, 1982, the daughter of Chaks and Anila Karuturi. After completing her work at Mendon High School, Rochester, NY in 2001, she entered the combined BS/MD program at George Washington University in Washington, DC. She completed her BS in Biology in 2004 and her MD in 2010. The next three years, she completed her internship and residency at the University of Pennsylvania in Philadelphia, PA. She then went on to complete her fellowship in Medical Hematology/Oncology at the University of Texas MD Anderson Cancer Center, Houston, Texas in 2014. In July of 2014, she started her full-time faculty position in breast medical oncology at MD Anderson Cancer Center.

Permanent Address:

2727 Revere Street, Apt 2099

Houston, TX 77098