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POTENTIALLY INAPPROPRIATE MEDICATIONS DEFINED BY STOPP CRITERIA IN OLDER PATIENTS WITH BREAST AND COLORECTAL CANCER

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Abstract

Purpose: Screening for potentially inappropriate medications (PIM) is recommended in older patients with cancer receiving chemotherapy, given the concern for adverse drug reactions, drug-drug interactions and non-adherence. Our objective was to determine the impact of PIM on outcomes in patients with breast and colorectal cancers receiving chemotherapy.

Methods: We used data from the SEER-Medicare database, including patients ≥ 66 years old with a diagnosis of Stage II/III breast and colorectal cancer made between 7/1/2007-12/31/2009. We used modified STOPP criteria to define baseline PIM as a dichotomous variable in the 4 months prior to diagnosis. STOPP criteria was used based on its performance as a robust measure of PIM. Outcomes measures included ER visits, hospitalizations, and death within 3 months from the last chemotherapy, and a composite of the three. We used Chi-square or Fisher's exact test to determine associations of PIM with covariates and outcomes, and Cox proportional hazards (PH) model for the time-to-event analysis.

Results: Final analysis included 1,595 patients with breast cancer and 1,528 patients with colorectal cancer. Frequency of baseline PIM by STOPP was 31.5% in the breast and 30.9% in the colorectal cohort. In the breast cohort, associations with the composite outcome in the Cox PH model included disease stage, comorbidity, medication number and baseline ER visits/hospitalization. Age, gender, race, comorbidity and baseline ER visits/hospitalization were

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associated in the colorectal cohort. PIM was not associated with outcomes in either cohort, aside from hospitalization in the breast.

Conclusions: We found no consistent association between pre-chemotherapy PIM defined by STOPP and outcomes.

Keywords

geriatric oncology; health outcomes; breast cancer; colorectal cancer; polypharmacy; inappropriate medications; STOPP criteria

Introduction:

Older adults with cancer are frequently prescribed multiple medications or medications deemed as potentially inappropriate (PIM), at rates ranging from 21–40%.^{1–3} PIMs are medications/classes of drugs with a high-risk to benefit ratio, such as sedatives and anticholinergics.⁴ Identification of PIM and/or polypharmacy at every visit through screening tools validated in the older adult populations, such as Beers⁵ or Screening Tool of Older Person's Prescriptions (STOPP) criteria⁶, is a strongly endorsed by the National Comprehensive Cancer Network Guidelines.⁷ Polypharmacy can be defined in many ways, but generally refers to the use of greater than 5 or more medications. The present guidelines encourage physicians to reconcile medication use with any tool, although there is lack of knowledge on which measure is best.

Amongst older adults without cancer, PIM has been shown to be associated with significant morbidity, adverse drug events, emergency room (ER) visits, hospitalization and mortality.^{4,8,9} However, it is unclear if these tools are associated with adverse outcomes in the older adult cancer population.

Most studies of PIM in older adults with cancer have employed the Beers list, but the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria can also be used to identify and reduce PIMs. The STOPP criteria evaluate for PIM by identifying drug-drug interactions, drug-disease interactions, drugs which increase the risk of falls, and drugs which duplicate therapy.⁹ The validity of STOPP over Beers aside from taking into account drug-disease interactions is that some prospective studies in hospitalized older adults without cancer show superiority of STOPP in identifying patients at greater risk for adverse drug events.⁹ Furthermore, studies looking at Beers criteria in older adults with cancer have not been found to impact overall outcomes.^{3,10} In our analysis, we sought to characterize the frequency of baseline PIM defined by STOPP criteria in older patients receiving adjuvant chemotherapy for breast and colorectal cancer. We then looked to evaluate the impact of PIM on important clinical outcomes, given the dearth of evidence to support the association and validate the present national guidelines for screening.

Methods:

We utilized the merged Surveillance, Epidemiology and End Results (SEER) Medicare database as our data source.¹¹ Individuals included were 66 years or older, diagnosed with

Stage II-III breast or colorectal cancer between July 2007 and December 2009, and received adjuvant chemotherapy. We chose patients only treated in the adjuvant setting for breast and colorectal cancer given known survival advantage of adjuvant chemotherapy in older adults, large representation of these two subtypes in particular, and in effort to create a more homogenous sample. The time-cut of utilized was based on available data at our institution. We required that beneficiaries had twelve months of continuous Medicare Parts A/B without health maintenance organization (HMO) enrollment before diagnosis and twelve months after diagnosis, or until death within twelve months following diagnosis. Furthermore, we required that beneficiaries had four months of continuous Medicare Part D enrollment before diagnosis to a time period of twelve months after diagnosis or until death within this period. We excluded individuals with a second cancer diagnosis within twelve months of first diagnosis, and those without a histologic confirmation. Clinical outcomes of interest were ER visits, hospitalization, death or a composite outcome that included all three. Medications were only captured if there was a prescription for at least 90 days' supply or a 30 days' supply with more than one refill. The study was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board (IRB).

Descriptive statistics were used to summarize PIM rates and other baseline sample characteristics. The exposure period for baseline PIM was from four months prior to diagnosis up to the date of diagnosis. Medications were counted if they were at least a 90 days' supply or a 30 days' supply with more than one refill. We also characterized the incidence of PIM in a pre-chemotherapy period (from the date of diagnosis to the first dose of chemotherapy), in addition to incidence from zero to three months and three to six months after starting chemotherapy. Demographic and clinical variables included age groups, race/ethnicity, sex, census tract-based educational and poverty level, stage, Charlson Comorbidity index, baseline polypharmacy (defined as ≥ 5 medications), and presence of ER visits/hospitalization in the pre-treatment time-period. Time-to event analysis utilizing Cox proportional hazards (PH) modeling was performed to determine whether baseline PIM, patient and clinical characteristics were associated with adverse outcomes. Patients were right censored at three months after the last chemotherapy.

STOPP criteria is specifically comprised of 65 commonly encountered instances of potentially inappropriate prescribing and are arranged by physiologic system.⁹ Given that STOPP criteria are usually applied prospectively, we were only able to include 48 due to limitations of the data-source. We utilized version one of the STOPP criteria in our study. Drug-disease interactions were identified using the appropriate International Classification of Disease (ICD-9) diagnosis or procedure codes. Previous studies have also demonstrated that STOPP criteria can be adapted to administrative data.⁶

Results:

In our analysis, we included 1,595 patients with breast cancer and 1,528 patients with colorectal cancer. Table 1 depicts baseline patient characteristics. The incidence of PIM utilizing STOPP criteria was 31.5% and 30.9% in the breast and colorectal cohorts accordingly. For both cohorts, the incidence of PIM decreased in the pre-chemotherapy time

period as well as the time period zero to three and three to six months after starting chemotherapy (Table 2).

In both cohorts, baseline PIM was generally not associated with adverse outcomes. In the time-to-event analysis for the breast cohort, the median follow-up was 5.7 months (Table 3). 42.9% of patients in the breast cohort had at least one ER visit, (one-year event free-rate of 49%) 23.1% at least one hospitalization (one-year event-free rate of 62%), 2.1% death (one-year event-free rate of 96%), and 37.5% a composite outcome (one-year event-free rate of 45%). Associations with the composite outcome (Table 4) included advanced stage (Hazard Ratio; HR 1.33, 95% CI 1.13–1.57, $p=0.001$), higher comorbidity index (HR 1.46, 95% CI 1.15–1.85, $p=0.002$), baseline polypharmacy (HR 1.75, 95% CI 1.34–2.28, $p<0.0001$), and baseline ER visits/hospitalization (HR 1.4, 95% CI 1.12–1.75, $p=0.004$). The only outcome with which baseline PIM was associated with was hospitalization in the breast cohort (HR 1.28, 95% CI 1.02–1.61, $p=0.032$). Polypharmacy was separately associated with ER visits (HR 1.73, 95% CI 1.31–2.29, $p=0.0001$) and hospitalization (HR 1.83, 95% CI 1.29–2.59, $p=0.001$), but not death.

In the colorectal cohort, the median follow-up was 5.9 months (Table 3).. The frequency of the outcomes included 40.6% for ER visits (one-year event-free rate of 42%), 29.5% for hospitalization (one-year event free rate of 54%), 5% for death (one-year event-free rate of 91%), and 45% for the composite outcome (one-year event-free rate of 38%). Associations with the composite outcome in the multivariable analysis (Table 4) included older age (HR 1.27, 95% CI 1.03–1.55, $p=0.022$), female gender (HR 1.37, 95% CI 1.18–1.6, $p<0.0001$), higher comorbidity index (HR 1.34, 95% CI 1.07–1.67, $p=0.01$), and baseline ER visit/hospitalizations (HR 1.17, 95% CI 1–1.38, $p=0.05$). Polypharmacy was associated with ER visits only (HR 1.23, 95% CI 1.04–1.47, $p=0.016$), but not hospitalization or death.

Discussion:

In this study, we found that PIM defined by STOPP criteria was prevalent, occurring in about 30% of patients with cancer receiving chemotherapy. However, we found no consistent association between PIM at baseline and adverse outcomes. Our findings are similar to previous studies. In their study, Maggiore and colleagues evaluated a heterogeneous population of patients prospectively and found rates of PIM defined by three indices (Beers, Zhan and Drugs to Avoid in the Elderly) of up to 29%, and no associations between PIM and grade 3 or 4 toxicities defined by CTCAE and hospitalization.³ Nightengale et al also evaluated a more heterogeneous group of patients, utilizing an older version of the STOPP criteria in addition to the 2012 Beers criteria and HEDIS DAE list.¹ They found rates of PIM of 38%, 40% and 21% respectively, but did not look at outcomes. In our study, the one positive association with baseline PIM was in the breast cohort in regard to baseline PIM and time-to-first hospitalization (HR 1.28, $p=0.003$). We also found that polypharmacy was associated with several adverse outcomes in both cohorts. We also identified that various patient characteristics and factors (such as higher stage of disease, older age, and comorbidity) were associated with adverse outcomes.

A major strength of our study was that we evaluated a large population of patients with similar disease processes and treatments. A weakness is the retrospective nature of our study. Furthermore, PIM was only captured in a cross-sectional way. We tried to account for this by only considering medications for which there was a 90-day supply or multiple refills. Furthermore, we had no way of confirming whether a patient actually took the prescribe medications. Finally, a major limitation is the inability to account for over-the counter medications, such as anti-histamines or non-steroidal anti-inflammatory drugs (NSAIDs), due to their exclusion from Part D data. Over-the counter medications have been captured in previous studies to be prevalent classes of PIM.⁷

The results of our study suggest that polypharmacy, but not PIM, is frequently associated with adverse outcomes in patients with cancer receiving chemotherapy. These findings are similar to an analysis we performed applying Beers criteria to the same dataset.¹² There are a few potential reasons for this finding. It is possible that patients discontinue PIMs once they are diagnosed with cancer and initiate chemotherapy. Our study supports this, given that incidence of PIM was seen to decrease in the time period following diagnosis. Additionally, supportive care medications considered to be PIM may provide more benefit than harm in this setting. PIM may only contribute a relatively small risk in addition to cancer and cancer therapy in older patients, and reduced PIM might not provide much incremental benefit. Furthermore, the association of PIM with adverse outcomes may depend on the amount and quantity of PIM exposure. Our findings are interesting, given that they question the emphasis that physicians need to place on PIM screening in older adult patients with cancer receiving chemotherapy. However, in order to uncover the true association, prospective studies are required that accurately capture PIM and adherence. Although we did factor in comorbidity utilizing the Charlson comorbidity score as a confounder in our multivariable model, such claims-based proxies for frailty are limited. Baseline data in future studies should also include the more robust components of the geriatric assessment that identify comorbidities and geriatric syndromes or additional claims-based proxies of frailty^{13–15} in order to better control for confounding factors related to comorbidity and frailty.

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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	0%	758(49.6%)
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%)

	Breast Cancer Cohort (N = 1595)	Colorectal Cancer Cohort (N = 1528)
11+	508(31.8%)	461(30.2%)
Chemotherapy regimen (breast cancer)		
Anthracycline-based	493(30.9%)	
Non-Anthracycline-based	1102(69.1%)	
Chemotherapy multi-regimen (colorectal cancer)		
No		670(43.8%)
Yes		858(56.2%)

Table 2:

Incidence of PIM

	Breast	Colorectal
Baseline	39%	30.9%
Pre-chemotherapy	36.6%	37.4%
0–3	27.9%	31.7%
3–6	20%	23.6%

Table 3:

Summary info for time (from first chemo) to event

	ER [*]	Hospitalization	Death	ER/Hospitalization/death
<u>Breast cancer</u>				
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)
<u>Colorectal cancer</u>				
Number of event (%)	621(40.6%)	450(29.5%)	76(5%)	687(45%)
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)

*
ER= Emergency Room visits

Table 4:

Cox PH Model for time-to-event (time-period of 3 months from start of chemotherapy; adjusted for year of diagnosis, poverty, education, number of care providers, chemotherapy regimen, baseline PIM, and baseline ER/hospitalization)

Cohort	HR*	95% CI*	p-value*
Breast			
Baseline PIM via STOPP criteria (yes v. no)	1.07	0.89–1.29	0.46
Stage III v. II	1.33	1.13–1.57	0.001
Charlson 2+ v. 0	1.46	1.15–1.85	0.002
5–10 v. 0–4 baseline medications	1.27	1–1.61	0.049
11+ v. 0–4 baseline medications	1.75	1.34–2.28	<0.0001
Colorectal	HR	95% CI	
Baseline PIM via STOPP criteria (yes v. no)	1.11	0.94–1.33	
Age 70–75 v. 66–70	1.27	1.03–1.55	0.022
other v. non-Hispanic white race	0.59	0.44–0.8	
Female v. male	1.37	1.18–1.6	<0.0001
Charlson 2 v. 0	1.34	1.07–1.67	0.01
Baseline ER/Hospitalization	1.17	1–1.38	0.05

* HR= Hazard ratio; CI= confidence Interval; p-value = calculated possibility