Incidence of Skeletal-Related Events in Men With Castration-Resistant Prostate Cancer

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BACKGROUND

- Skeletal-related events (SREs) are common in men with bone metastases and have negative consequences for patients with castration-resistant prostate cancer (CRPC), including pain, reduced quality of life, and increased risk of death.
- Published data on background rates of SREs in men with CRPC under routine medical care are sparse.

OBJECTIVE

- To estimate the incidence rates of SREs in a cohort of men with CRPC in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database

METHODS

Data Source

- The SEER-Medicare linked database is administered by the United States (US) National Cancer Institute.
  - Combines data from the SEER program, which collects population-based cancer registry data covering approximately 30% of the US population,[1] with data from Medicare, the US federal health insurance program primarily for people aged 65 years or older
  - Contains detailed information for each primary cancer and individual, including the initial diagnosis and date of death

Study Population

- Men aged ≥ 65 years in the SEER-Medicare database with a prostate cancer diagnosis in 2000-2011, who had surgical or medical castration, and who met the protocol-defined criteria for castration resistance and the following:
  - Had no prior malignancy (other than prostate cancer or nonmelanoma skin cancer)
  - Were enrolled in Medicare Parts A and B continuously for at least 1 year before initiation of second-line systemic therapy (i.e., cohort entry date) and from date of initial prostate cancer diagnosis until initiation of second-line systemic therapy
  - Had no evidence of treatment with radium-223 dichloride prior to the cohort entry date (though none was observed in the data)
- Castration resistant prostate cancer, defined as advanced prostate cancer progression despite medical or surgical castration, is identified in clinical practice using serum testosterone levels, prostate-specific antigen measurements, and results of bone imaging studies.[2]
- Because Medicare claims data lack biochemical and radiological data, castration resistance was inferred from the initiation of second-line treatments after surgical or medical castration, identified as follows:
  - Surgical castration (bilateral orchiectomy): Identified using algorithms for orchiectomy that were created for a prior study.[3]
  - Medical castration (androgen deprivation therapy): Identified with administrations or prescriptions for the following drugs: abarelix, bicalutamide, buserelin, cyproterone, degarelix, diethylstilbestrol, estramustine, flutamide, gonadorelin, goserelin, histrelin, leuprolide, medroxyprogesterone, megestrol, nafarelin, nilutamide, polyestradiol, or triptorelin. This list was adapted from the American Urological Association Guidelines.[4]
  - Initiation of second-line systemic therapies: Identified with the first occurrence of administrations or prescriptions of any of the following treatments: abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T.

Outcomes

- Primary outcome: SREs, defined broadly as fracture, bone surgery, radiation therapy, or spinal cord compression.
- Secondary outcomes: (1) fracture (pathologic or traumatic) and (2) pathologic fracture.
- Outcomes were identified in Medicare claims data.
- Patients entered the cohort on the date they were identified as first receiving a therapy representing a second-line systemic treatment for prostate cancer. On this date, follow-up began for the occurrence of an SRE.
- Follow-up time for each patient continued until the earliest occurrence of the following: SRE, death, second primary malignancy, discontinuation of Part A or Part B Medicare coverage, enrollment in a health maintenance organization, or the end of the study period.

Analysis

- Incidence rates of SREs (per 100 person-months) and 95% confidence intervals (CIs) were calculated in all eligible person-time following cohort entry (defined as the date of initiation of second-line treatment for prostate cancer).
- Incidence rates were also stratified by:
  - Person-time before and after first use of any of the following bone-targeted agents: alendronate, denosumab, ibandronate, pamidronate, risedronate, or zoledronic acid
    - Patients were identified on the basis of whether they used bone-targeted agents after the initial prostate cancer diagnosis.
      - If no use was identified after the initial diagnosis, all person-time was considered to be "before" first use.
      - If use was identified after the initial diagnosis, we identified whether first use was before or after cohort entry. We then categorized person-time into whether it occurred before or after first use.
  - History of SRE before cohort entry

RESULTS

Participants

- During the study period, 564,491 men were diagnosed with prostate cancer. Of those, 2,234 individuals met the protocol-defined criteria for CRPC and other eligibility criteria for the cohort.

Table 1. Demographic and Clinical Characteristics of the Study Cohort (N = 2,234)

Variable	Number of Patients (%)
Race	
White	1,867 (83.6)
Black	218 (9.8)
Asian	46 (2.1)
Hispanic	48 (2.1)
Other or unknown[a]	55 (2.5)
Age at cohort entry, years	
Mean (SD)	76.6 (6.2)
Distribution	
65-69	297 (13.3)
70-74	625 (28.0)
75-79	595 (26.6)
80-84	451 (20.2)
85+	266 (11.9)
SRE prior to cohort entry[b]	1,252 (56.0)
First use of bone-targeted agent prior to cohort entry[c]	1,213 (54.3)
First use of bone-targeted agent after cohort entry	326 (14.6)
No use of bone-targeted agents	695 (31.1)
Length of follow-up, months	
Mean (SD)	10.6 (11.6)
Distribution	
< 6 months	960 (43.0)
6 months to 1 year	590 (26.4)
> 1 to 1.5 years	317 (14.2)
> 1.5 to 2 years	152 (6.8)
> 2 years	215 (9.6)

SD = standard deviation.

[a] Categories were combined to avoid reporting a count of < 11.

[b] Identified in the Medicare Provider Analysis and Review file, carrier claims, or outpatient claims any time between the initial date of prostate cancer diagnosis and the cohort entry date.

[c] Identified any time between the initial date of prostate cancer diagnosis and the cohort entry date.

- The cohort was primarily white (83.6%), and the mean age at cohort entry was 76.6 years.
- More than half (56.0%) of the cohort had a history of SRE prior to cohort entry.
- Bone-targeted agent use in the cohort was common, with initial use before cohort entry in 54.3% of patients and initial use after cohort entry in 14.6% of patients.

Outcomes

Table 2. Demographic Characteristics of Patients With and Without SREs During Follow-up (N = 2,234)

Variable	Number of Patients With SRE (%) (N = 896)	Number of Patients Without SRE (%) (N = 1,338)
Race		
White	769 (85.8)	1,098 (82.1)
Black	72 (8.0)	146 (10.9)
Asian	16 (1.8)	30 (2.2)
Hispanic	12 (1.3)	36 (2.7)
Other or unknown[a]	27 (3.0)	28 (2.1)
Age at cohort entry, years		
Mean (SD)	75.5 (5.9)	77.3 (6.3)
Distribution		
65-69	143 (16.0)	154 (11.5)
70-74	293 (32.7)	332 (24.8)
75-79	231 (25.8)	364 (27.2)
80-84	156 (17.4)	295 (22.0)
85+	73 (8.1)	193 (14.4)

[a] Categories were combined to avoid reporting a count of < 11.

- SREs were common, with 40% of the cohort experiencing an SRE during follow-up.
- No substantial differences were observed in the race distribution of patients with and without SREs.
- Patients with SREs tended to be younger than those without SREs.
- Mean (SD) time from cohort entry to first SRE was 9 (10.1) months. More than half of the patients (74.3%) developed their first SRE within the first year after cohort entry, 18.3% within the second year after cohort entry, and 7.4% more than 2 years after cohort entry.

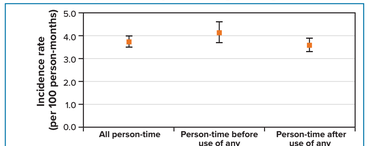
Table 3. Number of Cases of First SREs

SRE	Cases (% of Total Cohort)
Fracture	266 (11.9)
Bone surgery	22 (1.0)
Radiation	609 (27.3)
Spinal cord compression	37 (1.7)
Total	896 (40.1)

Notes: Cases identified using Medicare Provider Analysis and Review file, carrier claims (Physician/Supplier Part B), and outpatient claims. SREs on the date of the initial SRE during follow-up were counted. The sum of the cases of fracture, bone surgery, radiation, and spinal cord compression is greater than the total number of SRE cases, as patients may have had more than one type of SRE on the date of the first SRE.

- The most common types of SREs were radiation (occurring in 27.3% of the cohort) and fracture (11.9% of the cohort).
- Spinal cord compression and bone surgery were less common (each in < 2% of the cohort).

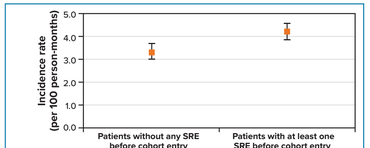
Figure 1. Incidence Rates of SREs and 95% Confidence Intervals (per 100 Person-Months) Among All Person-Time and Stratified by Use of Any Bone-Targeted Agent



	All person-time	Person-time before use of any bone-targeted agent	Person-time after use of any bone-targeted agent
Patients	2,234	1,021	1,539
Person-months	23,716	7,429	16,287
Cases	896	309	587

- The incidence rate of SREs in all person-time was 3.78 per 100 person-months.
- The incidence rate was numerically lower after use of any bone-targeted agent (before use: 4.16 per 100 person-months; after use: 3.60 per 100 person-months).

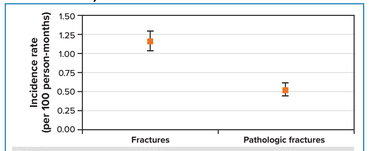
Figure 2. Incidence Rates of SREs and 95% Confidence Intervals (per 100 Person-Months) Among Patients Without or With an SRE Before Cohort Entry



	Patients without any SRE before cohort entry	Patients with at least one SRE before cohort entry
Patients	982	1,252
Person-months	11,549	12,167
Cases	385	511

- The incidence rate of SREs was numerically higher among patients with a history SRE than patients without such a history (4.20 per 100 person-months versus 3.33 per 100 person-months)

Figure 3. Incidence Rates of SREs and 95% Confidence Intervals of Fractures and Pathologic Fractures (per 100 Person-Months)



	Fractures	Pathologic fractures
Patients	2,234	2,234
Person-months	31,257	33,635
Cases	363	176

DISCUSSION

Strengths

- This analysis used the SEER-Medicare database, which is representative of the elderly population in the US and is the largest available source of detailed population-based medical information on men aged 65 years or older with prostate cancer.

Limitations

- Second-line treatment (after surgical or medical androgen deprivation therapy) was used to define CRPC because biochemical and radiologic data that directly indicate disease progression despite androgen deprivation therapy are not available in claims data.
- Diagnosis and procedure code algorithms in Medicare claims data were used to identify SREs. Claims codes for radiation do not specify the anatomic target, and codes for fractures may capture fractures due to causes other than pathologic processes (including trauma or osteoporosis).
- Because of potential bias due to confounding by indication, we did not perform any hypothesis testing or calculate any measures of association comparing rates before versus after bone-targeted agent use or in patients with versus without SREs before cohort entry.

CONCLUSIONS

- In this large cohort of elderly men with CRPC under routine medical care in the US, SREs were common, with most occurring within 1 year after cohort entry.
- Incidence rates of SREs were numerically lower following bone-targeted agent use and numerically higher among patients with a prior history of SREs.
- A direct causal interpretation of the difference in rates before versus after bone-targeted agent use or in patients with versus without SREs before cohort entry is not possible because confounding by indication and other factors cannot be excluded. However, further analysis may address at least some potential confounders.

DISCLOSURES

A. Kawai, C. Saltus, D. Martinez, and J. Kaye are employees of RTI Health Solutions, which received funding from Bayer HealthCare Pharmaceuticals, Inc. to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. RTI International conducts work for government, public, and private organizations, including pharmaceutical companies. Z. Vassilev and M. Soriano-Gabarro are employees of Bayer.

This study was conducted using data from NCI's SEER program of the US and guided by a data use agreement between NCI and RTI Health Solutions.

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