Risk of Vascular Toxicity with Platinum Based Chemotherapy in Elderly Patients with Bladder Cancer

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Purpose: Platinum based chemotherapy is widely used for bladder cancer but is associated with vascular toxicity, especially thromboembolism. We evaluated the short-term (less than 1 year) and intermediate-term (2 to 5 years) vascular toxicity of platinum agents in older patients with bladder cancer.

Materials and Methods: We identified Medicare beneficiaries 66 to 94 years old diagnosed with stage II-III bladder cancer from 1998 to 2007 in the SEER-Medicare database. We measured the association between platinum based chemotherapy and vascular events (thromboembolic and nonthromboembolic) using Cox proportional hazard regression models.

Results: The sample included 5,057 patients, of whom 21.3% received platinum based chemotherapy. Patients receiving platinum based chemotherapy were more likely to be younger and male with less comorbidity than those not receiving any chemotherapy. During the first year after diagnosis the patients who received platinum based chemotherapy had a higher risk of a thromboembolic event (19.8% vs 11.6%, AHR 1.43, 95% CI 1.17−1.75) compared to those who did not receive chemotherapy. The likelihood of having a thromboembolic outcome was similar whether platinum chemotherapy was cisplatin based (21.1%, AHR 1.56, 95% CI 1.22−2.00) or carboplatin based (18.9%, AHR 1.35, 95% CI 1.07−1.71). During years 2 to 5 after diagnosis there was no significant association between platinum chemotherapy and the risk of thromboembolic events. The risk of nonthromboembolic vascular events was not increased with platinum chemotherapy in either period.

Conclusions: Patients receiving platinum based chemotherapy were at higher risk for thromboembolism but not other vascular events, particularly in the first year after diagnosis. This risk of thromboembolism is similar for cisplatin and carboplatin.

Abbreviations and Acronyms

ACS = acute coronary syndrome
AE = arterial thromboembolism
AHR = adjusted hazard ratio
AMI = myocardial infarction
CM = cardiomyopathy
CVA = cerebrovascular accident
DVT = deep vein thrombosis
HF = heart failure
PE = pulmonary embolism
SEER = Surveillance, Epidemiology and End Results
TIA = transient ischemic attack

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For another article on a related topic see page 188.

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BLADDER cancer is predominantly a disease of the elderly with a median age at diagnosis of 73 years.[1] Platinum agents such as cisplatin and carboplatin are considered first line chemotherapy agents for bladder cancer.[2] Acute vascular toxicities, including angina and myocardial infarction,[3,4] arterial thromboembolism, deep venous thrombosis, pulmonary embolism, transient ischemic attack and cerebrovascular accident, are known to occur during or within a few weeks of treatment with cisplatin.[5,6] Data on the acute vascular toxicity of carboplatin are limited to case reports and meeting abstracts.[3,7] Among patients with bladder cancer the short-term risk of thromboembolism with cisplatin or carboplatin is estimated to be between 13% and 20% in retrospective or phase 2 studies.[6,8–11] The risk of thromboembolism may be higher if the platinum agents are combined with gemcitabine, which is frequently used in the treatment of urothelial cancer.[6,8,10]

While short-term outcomes after platinum therapy have been described, little is known about intermediate-term outcomes. Currently there are sparse data on short-term and no data on intermediate-term vascular effects of cisplatin in patients with bladder cancer. Even less is known about the vascular toxicity of carboplatin, even though carboplatin is used more frequently than cisplatin for bladder cancer.[2] Due to their advanced age and multiple comorbidities, patients with bladder cancer may be at high risk for vascular toxicity.

Accordingly, we evaluated the short-term (less than 1 year) and intermediate-term (up to 5 years) risks of vascular events in patients with bladder cancer who received platinum agents. We also assessed whether the risk varied by the type of platinum agent used.

MATERIALS AND METHODS

Data Sources

We used the SEER-Medicare linked database, which includes patient and tumor characteristics provided by SEER, as well as Medicare claims, to allow the ascertainment of cancer treatment, patient management and adverse events.[12,13]

Study Cohort

We selected patients 66 to 94 years old who were diagnosed with bladder cancer as their first or only cancer from 1998 to 2007. We only included patients 66 years old or older at diagnosis to ensure that there was at least 1 year of claims available before diagnosis to measure comorbidity. We only included patients with stage II or III disease at diagnosis because platinum chemotherapy is indicated for this group as primary treatment, either as an adjunct to surgery or combined with radiation. Patients with stage IV disease were excluded from analysis because poor prognosis may not allow adequate followup for the development of vascular toxicities.

We used exclusion criteria consistent with those of previous SEER-Medicare research (fig. 1). As SEER only reports the month of cancer diagnosis, we excluded patients with start of therapy or death recorded as before or during the month of diagnosis.[13]

Platinum Chemotherapy

We identified the administration of platinum based chemotherapy with cisplatin or carboplatin using the Healthcare Common Procedure Coding System (supplementary Appendix 1, http://jurology.com/). The exposure of interest was receipt of platinum chemotherapy in the first year of diagnosis compared with no chemotherapy. For the cleanest comparison we used patients who did not receive chemotherapy as the control group and excluded 167 patients who received non-platinum chemotherapy.

Outcomes

We ascertained vascular outcomes according to ICD-9-CM diagnosis codes in the 5 years after bladder cancer diagnosis (supplementary Appendix 1, http://jurology.com/). We assessed vascular outcomes individually and then categorized them into thromboembolic or non-thromboembolic events. Thromboembolic vascular events were pulmonary embolism/deep vein thrombosis/arterial thromboembolism, AMI/acute coronary syndrome/angina, CVA/TIA and sudden death. Nonthromboembolic vascular events included heart failure/cardiomyopathy, ventricular fibrillation/cardiac arrest and atrial fibrillation. We also assessed all cause mortality in the first year and years 2 to 5 after diagnosis. Details on patient censoring, outcome ascertainment, covariates and statistical analyses are given in supplementary Appendix 2 (http://jurology.com/).

RESULTS

Platinum Based Chemotherapy vs No Chemotherapy

Among the 5,057 patients with stage II and III bladder cancer, most were male (67.7%). Median age of the cohort was 78 years and the majority (66.4%) had stage II bladder cancer. Overall 1,079 (21.3%) patients received platinum based chemotherapy within the first year after diagnosis (table 1). Almost half (46.8%) of the patients who received platinum based chemotherapy also received gemcitabine in the first year after diagnosis. Compared with patients who did not receive chemotherapy, those who received platinum chemotherapy were younger