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Original article

Early chemotherapy discontinuation and mortality in older patients with metastatic bladder cancer: The AGEVIM multicenter cohort study

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Abstract

Purpose: Median age for the diagnosis of metastatic bladder cancer (MBC) is 73 years. The feasibility of chemotherapy in older patients is controversial. Our objectives were to assess associations linking age to first line chemotherapy regimen selection, early chemotherapy discontinuation, and 1-year mortality in everyday practice.

Materials and methods: Between 1999 and 2011, 197 consecutive patients aged ≥70 years with MBC referred to 4 hospitals were included in the AGEVIM multicenter cohort. At baseline, we recorded performance status (PS); tumor characteristics; the Charlson Comorbidity Index; and plasma creatinine, hemoglobin, and albumin. Early discontinuation data were available for 193 patients, and overall 1-year mortality for 180 patients. We assessed the probabilities of initial cisplatin-based combination chemotherapy (CCC), early discontinuation (≤2 cycles), and 1-year mortality, using multivariate logistic regression and Cox proportional hazards modeling.

Results: Among the 193 patients (mean age: 76 ± 4.3 y), with 2 metastatic site in median 43.5% received CCC, 36.3% gemcitabine and carboplatin, and 20.2% gemcitabine alone. The probability of CCC decreased with age independently from sex, PS, creatinine clearance, and Charlson Comorbidity Index ($P < 0.0001$), early discontinuation occurred in 24.9% of patients. Factors independently associated with global chemotherapy early discontinuation were age (adjusted odds ratio$_{\text{per additional year}} = 1.11$; 95% CI: 1.02–1.20; $P = 0.01$) and higher metastatic-site number (adjusted odds ratio$_{\text{per additional site}} = 1.45$; 95% CI: 1.08–1.95; $P = 0.01$). The number of patients was too small for a robust analysis of factors associated with early chemotherapy discontinuation in each chemotherapy regiment subgroup.

Independent predictors of 1-year mortality (median = 9.6 mo) were early discontinuation (adjusted hazard ratio [aHR] = 4.77 [2.85–7.96] when PS < 2 and 20.6 [9.43–44.82] when PS ≥ 2; $P < 0.0001$), albumin < 35 g/l (aHR = 3.06 [1.81–5.17], $P = 0.0001$), creatinine clearance < 30 ml/min (aHR = 2.96 [1.45–6.06], $P = 0.009$), and higher metastatic-site number (aHR = 1.34 [1.14–1.56], $P < 0.0001$).

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Conclusion: Less than half of older patients with MBC received initial CCC and 25% had ≤2 cycles of chemotherapy. Older age was associated with decreased CCC prescription, independently from known contraindications, and with global chemotherapy early discontinuation, but not with 1-year mortality.

Keywords: Discontinuation; Aged; Bladder cancer; Metastatic; Chemotherapy

1. Introduction

Bladder cancer is the second most common urologic malignancy after prostate cancer in Europe [1]. Nearly half of the patients are older than 75 years at diagnosis [2]. Metastatic relapse occurs in 25% of patients [3]. The optimal first-line treatment for metastatic bladder cancer (MBC) is cisplatin-based combination chemotherapy (CCC) [1,2,4–7]. Patients with contraindications to CCC (of which the most common are functional impairments [8], heart failure, and renal dysfunction) are often given combined gemcitabine and carboplatin instead [1,7]. Other alternatives include single gemcitabine and supportive care only [2,9]. Phase III clinical trials suggest similar chemotherapy feasibility in highly selected older patients and in younger patients with MBC [10]. Observational studies of colorectal cancer suggest that older patients may receive less aggressive treatment compared with their younger counterparts [11,12]. In bladder cancer, an observational study suggested that age was associated with decreased use of neoadjuvant chemotherapy [13]. Only limited data are available on chemotherapy selection, feasibility, and outcomes in older patients with MBC [10,14].

We hypothesized that chronological age independently predicted both failure to receive first-line CCC [13] and early chemotherapy discontinuation in older patients with MBC. The objectives were to assess whether age was independently associated with chemotherapy regimen selection, early chemotherapy discontinuation, or 1-year mortality in older patients with MBC in everyday practice.

2. Methods

Written informed consent was obtained from each patient. The study complied with the Declaration of Helsinki. The study protocol was approved by the Ile-de-France IV institutional review board of the Saint-Louis Teaching Hospital, Paris, France.

2.1. Study design

AGEVIM (AGE-VessIe-chiMiotherapie or Age-Bladder-Chemotherapy) is an open cohort of consecutive patients aged ≥70 years with histologically confirmed MBC in any of 4 French centers (including 3 cancer centers) in Lyon, Montpellier, Villejuif, and Créteil between January 1999 and December 2011. Consecutive patients eligible for the study inclusion were identified using the chemotherapy database on the day the first chemotherapy course was started. We did not include patients scheduled to receive supportive care only.

2.2. Data collection

At baseline, we recorded center, age, sex, and tumor characteristics at diagnosis and at inclusion (histology, grade, and location and number of metastatic sites); treatments (previous perioperative chemotherapy, surgery, or radiotherapy; chemotherapy regimen); performance status (PS); Charlson Comorbidity Index (CCI); smoking history; and pretreatment serum hemoglobin, albumin, and creatinine levels. Tumors were graded using the current WHO/ISUP system. Chemotherapy regimens were classified into 3 groups and they are as follows: CCC, for example, combined gemcitabine and cisplatin or combined methotrexate, vinblastine, adriamycin, and cisplatin; GnC, gemcitabine combined with carboplatin or oxaliplatin and other platinum-based regimens; and G, gemcitabine alone and other single-agent regimens. Normal functional status was defined as PS < 2. Moderate and severe renal dysfunction were defined as creatinine clearance < 60 ml/min and <30 ml/min, respectively, as estimated using the modification of the diet in renal disease (MDRD) algorithm [15].

2.3. Outcome measurements

The primary outcome was first-line CCC vs. other first-line regimens. Secondary outcomes included early chemotherapy discontinuation defined as ≤2 chemotherapy cycles [1], as assessed prospectively using 3 separate data sources, namely, the paper and electronic medical records and the hospital chemotherapy database. For all patients, each chemotherapeutic agent given during each cycle, as well as cisplatin dosage, was recorded prospectively by the pharmacist-in-charge at the time of chemotherapy delivery. Cisplatin dose was assessed as the relative dose intensity (RDI) computed as the delivered dose over the planned dose. The local investigators assessed responses using response evaluation criteria in solid tumors (RECIST) criteria. We recorded overall 1-year mortality defined as the time from treatment initiation to death, last follow-up within the first year, or the end of the first year, whichever occurred first.

2.4. Statistical analysis

Patient characteristics are described as number (%) for qualitative data and mean (±1 Standard Deviation) or