Second-Line Chemotherapy for Metastatic Urothelial Carcinoma: Importance of Lymph Node-Only Metastasis as a Prognostic Factor and Construction of a Prognostic Model

Samer Salah,[1] Jae-Lyun Lee,[2] Antonio Rozzi,[3] Hiroshi Kitamura,[4] Kazumasa Matsumoto,[5] Sandy Srinivas,[6] Rafael Morales-Barrera,[7] Joan Carles,[7] Rami Al-Wardat,[1] Kamal Al-Rabi,[1] Mohammad Maakoseh[1]

Abstract

We propose a prognostic model for patients with metastatic urothelial carcinoma who are eligible for second-line chemotherapy using pooled analysis of individual patient data from 7 second-line studies. We constructed a prognostic model that we subsequently validated on an independent series. Our proposed model could prove helpful for risk stratification of patients enrolled in future second-line trials.

Background: A prognostic model for patients with metastatic urothelial carcinoma (UC) progressing after platinum-based therapy was constructed from data from the phase III vinflunine trial. However, prognostic information for patients treated with other regimens is limited. **Materials and Methods:** We pooled individual patient data from 7 second-line studies and analyzed the influence of factors of interest on overall survival (OS) through univariate and multivariate analysis. A prognostic model was constructed, and data from an independent series were used for validation. **Results:** The data from 193 patients were pooled. The second-line chemotherapy regimen was single-agent taxane in 54 patients (28%), a platinum-based combination in 47 (24%), and a non-platinum combination in 92 (48%). On multivariate analysis, Eastern Cooperative Oncology Group performance status ≥ 1, hemoglobin < 10 g/dL, and metastatic patterns other than lymph node-only metastasis emerged as independent adverse prognostic factors. Patients with all 3 factors (poor risk), 1 to 2 factors (intermediate risk), and no factors (good risk) had a median OS of 3.1, 8.7, and 16.5 months, respectively ($P < .0001$). The corresponding median OS for the validation series ($n = 44$) was 3.3, 8.1, and 13.3 months ($P = .023$). Furthermore, platinum-based regimens were independently associated with an OS benefit compared with other regimens (hazard ratio, 0.31; 95% confidence interval, 0.18-0.53; $P < .0001$). **Conclusion:** We have proposed and validated a prognostic model for patients with metastatic UC who were eligible for second-line therapy. The proposed model could prove helpful for risk stratification. Furthermore, our data suggest that testing second-line platinum-based regimens in randomized trials is warranted.

Clinical Genitourinary Cancer, Vol. 14, No. 3, 255-60
Keywords: Cancer progression, Chemotherapy, Prognosis, Survival, Urothelial carcinoma

Presented at the 2015 American Society of Clinical Oncology Genitourinary Cancers Symposium, General Poster Session B: Prostate, Penile, Testicular, and Urethral Cancers, and Urothelial Carcinoma (abstract 309).

[1]Medical Oncology Department, King Hussein Cancer Center, Al-Jubeiha, Amman, Jordan
[2]Department of Oncology and Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea
[3]Medical Oncology Unit, Istituto Neurotraumatologico Italiano, Grottaferrata, Italy
[4]Department of Urology, Sapporo Medical University School of Medicine, Sapporo, Japan
[5]Department of Urology, Kitasato University School of Medicine, Kanagawa, Japan
[6]Department of Medical Oncology, Stanford University Medical Center, Stanford, CA
[7]Genitourinary, CNS and Sarcoma Tumor Unit, Vall d'Hebron University Hospital, Vall d' Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain

Submitted: Jun 21, 2015; Revised: Oct 5, 2015; Accepted: Oct 17, 2015; Epub: Oct 24, 2015

Address for correspondence: Samer Salah, MD, Medical Oncology Department, King Hussein Cancer Center, Queen Rania Al-Abdullah Street, Al-Jubeiha, Amman 11941, Jordan
E-mail contact: ssalah-salah@hotmail.com

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2015.10.006

Introduction

Data addressing optimal second-line chemotherapy for metastatic urothelial carcinoma (UC) are scarce.[1-3] The limited number of randomized phase III trials has been considered a major factor for the limited data. Only 2 published phase III randomized trials have assessed second-line chemotherapy for metastatic UC.[4,5] This limited number has resulted from the difficulty in patient accrual owing to factors such as advanced age, comorbidities, impaired renal function, and rapid deterioration of performance status (PS).[6]

Although many phase II studies have assessed second-line chemotherapy for metastatic UC,[7-14] serious limitations in eligibility and heterogeneity in patient and disease characteristics have influenced data interpretation.[6] For instance, some studies have grouped 2 patient populations, in which 1 received second-line chemotherapy after front-line chemotherapy in a metastatic setting, and the other received second-line chemotherapy for metastasis after first-line chemotherapy in a perioperative setting (mixing different lines of treatment).

An important limitation of the 2 published second-line phase III trials was the absence of a stratification system at their initiation. Thereafter, a prognostic model was constructed using the data from patients enrolled in the phase III vinflunine trial.[15] Nevertheless, that model was derived from data from patients enrolled in a clinical trial investigating 1 type of second-line chemotherapy, which could limit the generalizability and applicability to patients treated with other regimens.

In the present pooled analysis, we assessed the survival outcomes of patients with metastatic UC who had been treated with variety of second-line regimens. We used a uniform definition of second-line chemotherapy and uniform eligibility criteria to overcome the aforementioned limitations. In addition, we have proposed a prognostic model that can be used for risk stratification. Furthermore, we attempted to validate the data on an independent series treated in a real world setting.

Materials and Methods

Search for Relevant Studies

We searched PubMed for studies assessing second-line chemotherapy for metastatic UC using 2 search strategies (Table 1). No limitations were used in regard to language or year of publication. The corresponding authors were contacted by electronic mail and asked to provide the individual patient data.

To be eligible, the patients were required to have received 1 line of previous therapy in the metastatic setting. However, previous perioperative chemotherapy was not a reason for exclusion.

Definitions

We defined second-line therapy as chemotherapy given in the second-line setting for disease progression after platinum-based regimens given in the first-line setting for metastasis.

Overall survival (OS) was calculated from the initiation of second-line chemotherapy until the last follow-up examination or death. Progression-free survival (PFS) was defined as the interval from initiating second-line chemotherapy to the first documentation of disease progression, the last follow-up examination, or death.

Table 1 Search Strategy for Studies Assessing Second-Line Chemotherapy for Metastatic Urothelial Cell Carcinoma

Variable	Search Strategy 1[a] (n)	Search Strategy 2[b] (n)
Search results	131	103
Irrelevant topics	54	29
Reviews	34	19
Guidelines	5	2
Duplicates	1	2
Case reports	0	2
First-line studies	2	3
Third-line studies	2	2
Phase I studies	0	1
Eligible studies	33	43[c]

Overall, 54 studies were eligible; we were able to access individual patient data from 7 studies, which were included in the pooled analysis.
[a]MeSH terms: "second line" AND "chemotherapy" AND "bladder cancer."
[b]MeSH terms: "second line" AND "transitional cell carcinoma."
[c]Of the 43 studies, 22 were duplicates from search strategy 1 and were excluded); 21 remained eligible.

Statistical Analysis

Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. We tested the possible influence of factors at the initiation of second-line therapy on OS through univariate analysis. These factors included age, gender, ECOG PS, serum hemoglobin, liver metastasis, lymph node (LN)-only metastasis, the receipt of previous definitive therapy, previous administration of perioperative chemotherapy, number of metastatic sites, the presence of bone metastasis, the presence of visceral metastasis, and the presence of lung metastasis. Factors with $P < .05$ were considered statistically significant. All factors with $P < .05$ were tested in the multivariate backward stepwise Cox regression analysis. Heterogeneity between the patient characteristics was measured using a fixed-effect model and expressed using the χ^2 test.

A prognostic model was constructed using the number of independent prognostic factors and was tested on an independent series of patients treated at a single institution. In addition, the following therapy-related factors were assessed for a possible influence on OS: freedom of progression at 6 months after initiating second-line chemotherapy, interval from first- to second-line chemotherapy, single-agent or combination second-line chemotherapy, and platinum-, anthracycline-, or ifosfamide-based second-line chemotherapy. The chemotherapy-related factors that exerted a statistically significant influence on OS were included, along with the independent factors identified in the first multivariate analysis, in a second multivariate Cox regression analysis. All statistical analyses were performed using SPSS, version 17 (SPSS Inc, Chicago, IL).

Results

Eligible Studies and Patients

According to our search strategy (Table 1), we identified 54 eligible studies. We were able to collect individual data for 226 patients from 7 studies.[7,9,12-14,16,17] Of the 226 patients, 33 were excluded because they had received second-line chemotherapy as