Improved 5-Factor Prognostic Classification of Patients Receiving Salvage Systemic Therapy for Advanced Urothelial Carcinoma

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Purpose: Prognostic factors in patients receiving salvage systemic therapy for advanced urothelial carcinoma include performance status, liver metastasis, hemoglobin and time since chemotherapy. We investigated the impact of albumin, and neutrophil, lymphocyte and platelet counts.

Materials and Methods: Patient level data from 10 phase II trials were used. Cox proportional hazards regression was applied to evaluate associations with overall survival. An optimal regression model was constructed using forward stepwise selection and risk groups were defined using the number of adverse factors. Trial was a stratification factor. External validation was done in a separate data set of 5 salvage phase II trials.

Results: Discovery data were obtained on 708 patients. After adjustment for the 4 known factors a platelet count of the upper limit of normal or greater and albumin less than the lower limit of normal were significant poor prognostic factors. Only the addition of albumin was externally validated. For 0 or 1, 2 and 3 or greater risk factors median overall survival was 8.9, 6.4 and 4.5 months in 207, 171 and 113 patients in the discovery data set of 491, and 10.6, 10.0 and 7.0 months in 73, 47 and 47 patients, respectively, in the validation data set of 167. By adding albumin the c-index improved from 0.610 to 0.639 in the discovery set and from 0.616 to 0.646 in the validation set.

Conclusions: Albumin was externally validated as a prognostic factor for overall survival after accounting for time from prior chemotherapy, hemoglobin, performance status and liver metastasis status in patients receiving salvage systemic therapy for advanced urothelial carcinoma. The discovery of molecular prognostic factors is a priority to further enhance this new preferred 5-factor clinical prognostic model.

Key Words: urinary tract, urothelium, carcinoma, albumins, prognosis

Abbreviations and Acronyms

CRP = C-reactive protein
ECOG = Eastern Cooperative Oncology Group
GPS = Glasgow prognostic score
Hb = hemoglobin
LLN = lower limit of normal
LM = liver metastasis
NLR = neutrophil-to-lymphocyte ratio
OS = overall survival
PS = performance status
TFPC = time from prior chemotherapy
UC = urothelial carcinoma
ULN = upper limit of normal

THE survival outcomes of patients receiving salvage therapy for advanced UC differs based on baseline prognostic factors. A 3-factor prognostic model consisting of ECOG PS greater than 0, Hb less than 10 gm/dl and LM was proposed by Bellmunt et al.[1] Thereafter the addition of a fourth factor, TFPC, to the mentioned 3 factors was reported to enhance the prognostic classification.[2] However, these models do not provide optimal discrimination of survival and there remains substantial room for improvement.

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A rationale may be offered to investigate the prognostic impact of other readily available candidate laboratory prognostic factors. These candidate factors include the neutrophil count, lymphocyte count, platelet count and albumin since they have been demonstrated to be prognostic in other advanced solid malignancies.[3,4] Moreover, in the context of first line platinum based chemotherapy for advanced UC the inclusion of hypoalbuminemia or leukocytosis enhanced separate prognostic models.[5,6] Therefore, we retrospectively analyzed a large pooled data set of prospective phase II trials to evaluate the impact of these candidate variables in the salvage therapy setting of advanced UC independent of previously established factors, ie Hb, PS, LM and TFPC.

PATIENTS AND METHODS

Patient Population

Ten prospective phase II trials of salvage systemic chemotherapy and/or biological agent therapy following platinum based chemotherapy for advanced UC were pooled in the discovery data set (supplementary table, http://jurology.com/).[7–15] These 10 trials were used to discover the potential role of selected new risk factors because they were already available and had been previously used for other retrospective analyses. Thereafter 5 other phase II trials of salvage therapy were pooled in the validation data set (supplementary table, http://jurology.com/).[16–20] All of these trials required previous pathological confirmation of UC and the presence of measurable metastatic disease. Trials performed after 2000 were selected based on the availability of individual patient level data and the willingness of the respective principal investigators to provide these data. Data on neutrophil count, lymphocyte count, platelet count and albumin were required in addition to TFPC, Hb, ECOG PS and LM status. Data were de-identified and provided in an Excel® spreadsheet by all investigators. Included trials were approved by the institutional review boards of the respective institutions. This retrospective study was performed after receiving approval at University of Alabama-Birmingham for retrospective analyses of such patients.

Statistical Methods

OS, the primary clinical end point, was calculated from the date of study entry until death from any cause. Objective tumor assessment was performed using RECIST (Response Evaluation Criteria in Solid Tumors) 1.0 in all trials[21,22] except the trial by Necchi et al, which evaluated pazopanib using RECIST 1.1.[12] Time to event outcomes were calculated using the Kaplan-Meier method. Cox proportional hazards regression was used to evaluate the association of neutrophil count, lymphocyte count, platelet count and albumin with OS adjusted for PS, Hb, LM and TFPC. Neutrophil count, lymphocyte count, platelet count and albumin were dichotomized as less than LLN, or ULN or greater. The LLN and ULN used uniformly for these variables were neutrophils 1,500 and 7,000, lymphocytes 1,000 and 3,000, and platelets 150,000 and 400,000 cells per mm^3, and albumin 3.5 and 5.5 gm/dl, respectively.

Trial was included as a stratification factor throughout. Patients in the trial of Choueiri et al who received docetaxel with or without vandetanib were included as 1 trial when stratifying for our analysis since there were no significant differences in OS between these arms.[7] Because patients in the trial by Gallagher et al received sunitinib administered in 2 doses and schedules (50 mg daily for 4 of every 6 weeks or 37.5 mg daily continuously), the different regimens were assigned a separate stratification.[11] Internal validation was performed using bootstrap methods with 95% bias corrected and accelerated CIs, p values and concordance statistics (c-index) calculated. External validation involved applying the risk groups defined from the development data set to the validation data set. All tests were 2-sided with $p \leq 0.05$ considered statistically significant.

RESULTS

Patient Characteristics

In the discovery data set 682 of 708 patients overall were evaluable for this analysis with available PS, Hb, LM and TFPC status. The neutrophil count, lymphocyte count, platelet count and albumin were available in 631, 554, 649 and 491 patients, respectively. A total of 444 patients had data on all 8 variables. Data were available on all evaluated variables in all 167 patients in the validation data set, including PS, Hb, LM, TFPC, platelet count and albumin. There was no statistically significant difference ($p > 0.05$) between the discovery and validation data sets in patient age, gender, ECOG PS or platelet count ULN or greater. Median OS in evaluable patients in the discovery and validation data sets was 6.8 (95% CI 6.0–7.0) and 9.4 months (95% CI 8.7–10.0), respectively ($p < 0.001$). In the discovery data set median TFPC was longer (4.4 vs 2.7 months, $p < 0.001$) and more patients had LM (34% vs 22%, $p = 0.002$). In the validation data set more patients had albumin less than LLN (32% vs 16%, $p < 0.001$) and Hb less than 10 gm/dl (37% vs 14%, $p < 0.001$).

Evaluations

Univariable Analysis of Impact of Factors on OS. Univariable analyses in the discovery data set identified 7 factors significantly associated with OS, including PS, Hb, LM, TFPC, neutrophils ULN or greater, platelets ULN or greater and albumin less than LLN (table 1). NLR was also significantly associated with OS but NLR was not investigated further as it was not observed to add additional information beyond neutrophils alone.

Multivariable Analysis of Independent Impact of Factors on OS. Only platelets ULN or greater and albumin