**Impact of contemporary patterns of chemotherapy utilization on survival in patients with advanced cancer of the urinary tract: A Retrospective International Study of Invasive/advanced cancer of the urothelium (RISC).**

Aristotelis Bamias,1 Kimon Tzannis,1 Lauren C. Harshman,2 Simon Crabb,3 Yu-Ning Wong,4 Sumanta Kumar Pal,5 Ugo De Giorgi,6 Sylvain Ladoire,7 Neeraj Agarwal,8 Evan Y. Yu,9 Guenter Niegisch,10 Andrea Necchi,11 Cora N. Sternberg,12 Sandy Srinivas,13 Ajjai Alva,14 Ulka Vaishampayan,15 Linda Cerbone,12 Michalis Liontos,1 Jonathan Rosenberg,16 Thomas Powles,17 Joaquim Belmunt,2 Matthew D. Galsky,18 RISC Investigators.

1.Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 2.Dana-Farber Cancer Institute, Boston, MA, USA, 3.University of Southampton, Southampton, United Kingdom, 4.Fox Chase Cancer Center, Philadelphia, PA, USA, 5.City of Hope Comprehensive Cancer Center, Duarte, CA, USA, 6.IRCCS Istituto Scientifico Romagnolo per lo studio e la Cura dei Tumori, Meldola, Italy, 7.Center Georges-François Leclerc, Dijon, France, 8.University of Utah, Salt Lake City, UT, USA, 9.University of Washington, Seattle, WA, USA, 10.Heinrich-Heine-University, Düsseldorf, Germany, 11.Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, 12.San Camillo Forlanini Hospital, Rome, Italy, 13.Stanford University School of Medicine, Stanford, CA, USA, 14.University of Michigan, Ann Arbor, MI, USA, 15.Karmanos Cancer Institute, Detroit, MI, USA, 16.Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 17.Barts Health and the Royal Free NHS Trust, Queen Mary University of London, London, United Kingdom, 18.Mount Sinai School of Medicine, Tisch Cancer Institute, New York, NY, USA

Funding: This work was not supported by any grant funding.

Corresponding author: Aristotelis Bamias MD PhD MRCP, Dept of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece. Tel +30 2132162845. Fax +30 2132162511. Email: [abamias@med.uoa.gr](mailto:abamias@med.uoa.gr)

**Running Title:** Chemotherapy utilization in urinary tract cancer

This work has been presented in part at the ESMO Conference 2016, Copenhagen

Word count (text): 2496

Figures 2

Tables 4

Supplementary tables 4

Supplementary figures 1

**Abstract (word count: 299)**

**Background**

Cisplatin-based combination chemotherapy is the standard treatment for advanced urinary tract cancer (aUTC) but 50% of patients are ineligible for cisplatin according to recently published criteria.

**Objective**

To study patterns of chemotherapy utilization in real-world patients with aUTC and determine their impact on survival.

**Design, settings and participants**

Retrospective study of patients with: UTC (bladder, renal pelvis, ureter or urethra); stages T4b and/or N+ and/or M+; urothelial, squamous or adenocarcinoma histology, who received 1st-line chemotherapy, were selected.

**Outcome measurements and statistical analysis**

Primary objective: overall survival (OS). Eligibility-for-cisplatin criteria: Eastern Cooperative Oncology group (ECOG) performance status (PS)<1, creatinine clearance (CrCl)>60 ml/min, no hearing loss, no neuropathy, no heart failure. Cox regression multivariate analyses were used to establish independent associations of the type of chemotherapy (cisplatin vs. non-cisplatin) and eligibility-for-cisplatin on OS.

**Results and Limitations**

1426 patients treated between 2000 and 2013 were analyzed. Median follow-up: 31 months. Type of 1st-line chemotherapy: cisplatin-based 722 (50.6%), carboplatin-based 428 (30%), other 276 (19.4%). 25% of patients who did not receive cisplatin were eligible for this agent. Main reasons for this deviation: advanced age, co-morbidities. Cisplatin use and eligibility-for-cisplatin were independent favorable prognostic factors (Hazard ratio [HR]: 1.43, 95% confidence interval [CI]: 1.19-1.71; HR: 1.51, 95% CI: 1.31-1.87). Eligible-for-cisplatin patients treated with cisplatin lived longer than those who were not (HR: 2.05, 95% CI: 1.59-2.64). Median OS of ineligible patients was poor (9.8 months) irrespective of the chemotherapy used.

**Conclusions**

Published criteria of eligibility-for-cisplatin were validated in a multinational, real-world setting in aUTC. The reasons for deviations from these criteria set targets to improve adherence. Effective therapies for cisplatin-ineligible patients are needed.

**Patient Summary**

The outcome of patients with aUTC is associated with their eligibility for cisplatin-based combination chemotherapy. Therefore, avoiding deviations from criteria defining eligibility should be sought in everyday practice.

**Introduction**

Cisplatin-based chemotherapy is the treatment of choice in aUTC. Nevertheless, about 50% of treated patients do not receive cisplatin1,[2](#_ENREF_2) mainly due to concerns of increased toxicity and/or limited efficacy in certain patient groups. Instead, carboplatin is a preferred agent in the communitydue to its more favourable toxicity profile and ease of administration. The absence of level I evidence establishing the superiority of cisplatin over carboplatin and lack of well-established criteria defining patients likely to benefit from cisplatin instead of carboplatin-based therapy may encourage this tendency. This uncertainty is also reflected by the inherent eligibility criteria used in carboplatin-based chemotherapy in phase II studies.[3-8](#_ENREF_3)

Recently, specific criteria for eligibility-for-cisplatin have been proposed by Galsky et al.[9](#_ENREF_9) Although the criteria are widely accepted, their impact has not yet been formally assessed. In addition, adherence to these criteria outside the context of clinical trials has not been studied. In a recent report, 25% of patients with aUTC, treated at 10 Greek Oncology centers, did not receive cisplatin-based chemotherapy, although they were eligible according to Galsky’s criteria.[10](#_ENREF_10) The effect of deviations from these criteria on patients’ outcomes remains unknown.

We attempted to map the different practice patterns in aUTC and the reasons behind those practices as well as their impact on patient outcomes. We used the Retrospective International Study of Cancers of the Urothelium (RISC) database, the largest multinational database of UTC patients worldwide. This database includes data from hospitals in the United States, Europe, Israel and Canada thus ensuring an adequately wide representation of contemporary trends in the treatment of UTC.

**Patients and methods**

*Patients*

The RISC database includes patients with localized muscle-invasive or advanced UTC (defined as primary carcinoma of the urinary bladder, renal pelvis, ureter or urethra).11-13 Data were collected using a web-based electronic data capture tool. Data fields were centrally reviewed and queries were subsequently completed by each participating site. For the current study, patients were selected according to the following criteria: a) advanced UTC defined as metastatic disease or non metastatic inoperable disease, i.e. clinical stages T4bN0M0, TanyN+M0 and TanyNanyM+; b) histological subtype of pure or mixed urothelial carcinoma, pure squamous or pure adenocarcinoma; c) patients should have received 1st-line chemotherapy for aUTC. Administration of chemotherapy for radiosensitization purposes only was not considered as 1st-line chemotherapy. Patients with no information regarding the type of 1st-line chemotherapy were also excluded.

Database was locked in October 2015. The study was approved by the ethics committees at each participating institution.

*Statistical analysis*

OS was the primary variable, while the study of types of chemotherapy used and the impact of eligibility-for-cisplatin on chemotherapy utilization were the secondary end points. Eligibility-for-cisplatin was defined according to the criteria of Galsky et al9: ECOG-PS 0 or 1, calculated (Cockroft-Gault formula) CrCl≥60 ml/min, no hearing loss, no heart failure, no significant neuropathy. Centers were categorized according to the volume of aUTC patients. High-volume was arbitrarily defined as a minimum contribution of 100 patients with advanced disease in the database. Disease was categorized as lymph-node/local (LNL) only (including only bladder or local relapse and/or lymph node metastases) and distant (presence of non-lymph node metastases). Patients’ characteristics were presented through means, medians and proportions. Association between these characteristics and type of therapy was assessed by chi-squared test.

OS was defined as the time between the initiation of 1st-line chemotherapy and the date of death from any cause. Alive patients were censored at the date of last contact. Survival curves were estimated using the Kaplan-Meier method. Factors studied for their prognostic ability are listed in the Supplementary Table 1. To account for missing values multiple imputation was employed using the Markov Chain Monte Carlo method for Arbitrary Missing Data (number of imputations was 35). The association of these factors with OS was assessed through HRs estimated from univariate Cox proportional hazards models. Factors for which HRs were statistically significant at the level of significance 0.15 were then included in a multivariate Cox proportional hazards model. The backward selection procedure with removal criterion p>0.05 was performed to identify significant variables. Proportional hazards (PH) assumption was graphically assessed using plots of -ln{-ln(survival)} curves for each category of the covariates versus ln(analysis time). PH assumption was further tested on the basis of Schoenfeld residuals (vs time), globally and for each predictor separately (tests of the non-zero slope developed by Therneau and Grambsch). Maximum analysis time to be graphed was selected at 5 to 6 years. Patients alive at 5-6 years (regardless of subsequent death) were censored at that time. All analyses were carried out in STATA/SE 14.2 (StataCorp LP).

**Results**

*Population included in the analysis*

The flow chart of our analyses is depicted in Figure 1. From 3024 patients included in the RISC database, 1980 were treated for advanced disease at 29 centers between 2000 and 2013 and 1426 were suitable for the analysis of treatment patterns. Their median age was 67.5 years (range: 32-92), median time from diagnosis of UTC to diagnosis of advanced disease 0.36 years (range 0-20) and median CrCl 62.8 ml/min. Post chemotherapy surgery was reported in 77 patients (5%). Survival data were available for 1361 patients who were included in the survival analyses. Objective tumor responses to 1st-line chemotherapy were reported in 62% of the 1263 assessable patients. Complete responses were significantly more frequent among cisplatin-treated patients (11% vs 4%, p=0.03).

*Treatment patterns*

Cisplatin-based 1st-line chemotherapy was administered to 722 patients, carboplatin-based to 428 and other therapies to 276. Baseline characteristics of each chemotherapy group are shown in Table 1 and detailed description of systemic therapy administered is shown in Supplementary Table 2. Cisplatin administration was associated with younger age, male gender, less frequent neoadjuvant chemotherapy, better PS and renal function, less frequent distant metastases and high-volume centers. Cisplatin-treated patients also had a lower CCI: specifically, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), congestive heart failure (CHF), hyperlipidaemia and cerebrovascular disease (CVD) were less frequent among cisplatin-treated patients (Supplementary Table 3).

*Eligibility-for-cisplatin*

The reason for using carboplatin instead of cisplatin was provided by the investigators in 138 cases. The reasons quoted were: comorbidities (n=38), impaired renal function (n=156), poor PS (n=20), previous exposure to cisplatin (n=13), participation in clinical study (n=3), hearing loss (n=2), pre-existing neuropathy (n=1) and concerns about toxicity (n=6). Comorbidities included CHF in only 3 cases, while the remaining included a variety of conditions with COPD being the more frequent (n=10). Advanced age was also quoted in 51 cases. The patients of this group were significantly older than the patients receiving cisplatin (mean age: 78 vs. 64, p<.001)

Adequate data to assess eligibility-for-cisplatin according to Galsky’s criteria[9](#_ENREF_9) were available for 971 patients: 550 patients (56%) had at least one criterion for ineligibility (Supplementary Figure 1). The most common criterion was CrCl<60 ml/min (80%) followed by PS>2 (35%). Bone (32% vs. 23%, p=0.003) and distant metastases (58% vs. 51%, p=0.032) were more frequent in ineligible-for-cisplatin patients. There was also a strong correlation with the MSKCC risk stratification: all eligible-for-cisplatin patients were of low/intermediate risk, while only ineligible patients were included in the high-risk group. The distribution of eligible patients across different treatment groups is shown in Table 2. One hundred-twenty-seven patients (25%) who did not receive cisplatin were eligible for this agent. This deviation from Galsky’s criteria was more frequent in low volume centers (eligible patients not receiving cisplatin 28% vs. 15%, p=0.006) and in patients with: CCI>3 (46% vs. 23%, p<0.001), MSKCC intermediate/high risk (35% vs. 23%, p=0.006), hypertension (47% vs. 21%, p<0.001), diabetes (57% vs. 27%, p<0.001) and COPD (59% vs. 27%, p=0.001). Interestingly, 186 patients (38%) who received cisplatin fulfilled at least one criterion for ineligibility: CHF (n=10), ECOG-PS>1 (n=52), CrCl<60 ml/min (n=124).

*Survival analyses*

Among the 1361 patients included in these analyses 901 were dead at the time of analysis (disease: 804, toxicity: 9, other causes: 28, unknown reason: 60). Median follow up time was 31.4 months.

Cisplatin-based chemotherapy and eligibility-for-cisplatin were associated with significantly longer median OS, (Table 3, Figures 2a,b). Univariate analysis showed that bone, liver, lung and distant metastases, smoking history, CCI>3, ECOG-PS (0 vs. 1+2 and 0+1 vs. 2), wbc>10,000/mm3, plt>450,000/mm3, hemoglobin<inst. limit, albumin<median, age>median and increasing MSKCC score were adverse prognostic factors, while the presence of lymph node metastases and BMI>median were favorable prognostic factors. BMI, wbc, plt, hemoglobin and albumin, studied as continuous variables, were also significant prognostic factors. When these factors were entered into a multivariate cox regression model including therapy group (cisplatin vs. non-cisplatin) the latter retained its significance (Table 4). Similar results were obtained when eligibility-for-cisplatin was included in the model (Table 4) instead of therapy group. In the latter model PS and MSKCC category were excluded because PS is included in the criteria for eligibility-for-cisplatin and MSKCC. The independent prognostic significance of treatment type and eligibility-for-cisplatin were retained when multiple imputations for missing values were applied (Supplementary Table 4).

i. Subgroup analyses

Analyses investigating the significance of treatment patterns among the eligible or ineligible-for-cisplatin as well as other subgroups of prognosis and comorbidities are shown in Figures 2c-g, while the respective median OS and HRs are shown in Table 3.

Cisplatin-based chemotherapy was associated with a survival benefit among eligible patients, while outcomes of patients receiving carboplatin or other therapies were comparable (Figure 2c). Among ineligible patients the superiority of cisplatin over non-cisplatin-treated patients was due to a significantly longer OS over non-cisplatin/non-carboplatin therapy (median OS: 12, 95% CI: 10.8-14.3 vs. 6.8, 95% CI: 5.3-8.3; HR 1.60, 95% CI: 1.22-2.09; p<0.001), while no significant difference over carboplatin-based chemotherapy was observed (median OS: 12, 95% CI: 10.8-14.3 vs. 9.5, 95% CI 8.5-10.9; HR 1.26, 95% CI: 0.99-1.59; p=0.054) (Figure 2d). In concert with these findings, eligibility-for-cisplatin was associated with improved outcome only among cisplatin-treated patients (Table 3, Figure 2e). The interaction test between treatment type and eligibility-for-cisplatin yielded a significant result (p=0.033). Among the three MSKCC risk groups, only patients of low or intermediate risk benefited from cisplatin-based chemotherapy (Table 3, Figure 2f). Again, the interaction between treatment type and MSKCC category was significant (p=0.039).

Finally, benefit from cisplatin was obtained across all categories of co-morbidities studied (Figure 2g).

**Discussion**

This is the first study to describe international practice patterns and their effect on the outcome of patients with aUTC. The study has certain limitations associated with its retrospective nature: inaccuracies in reporting and reporting biases cannot be completely excluded, in spite of the performed quality control of the data. In addition, most centers contributing to the RISC database are referral centers for UTC and, therefore, community practice is not fully represented. In spite of these limitations, our data are original and potentially useful for clinical practice and future research. Apart from the depiction of practice patterns across countries with different health and insurance systems, the RISC database enabled the study of so far unexplored subjects, such as the comparison between cisplatin and carboplatin, as well as the value of the recently established criteria of eligibility-for-cisplatin and the impact of deviations from these criteria on outcome. Given that a randomized study, directly comparing cisplatin with carboplatin is unlikely, this analysis provides the highest possible level of evidence to this question, while it also provides useful benchmarks of the outcome of the various subgroups of patients with aUTC.

Fisty-six % of patients were ineligible-for-cisplatin. The distribution of the different criteria are strikingly similar among our study, a Greek cohort study[10](#_ENREF_10) as well as a recently reported phase II study.1[4](#_ENREF_11) This similarity supports the validity of these criteria and their applicability in the context of clinical trials. Interestingly, in another phase II study, the percentage of hearing impairment was higher1[5](#_ENREF_12) underlying the importance of excluding this factor by specific questioning.

Twenty-five % of patients not receiving cisplatin were eligible for this agent. This deviation was mainly due to advanced age and co-morbidities, especially hypertension, diabetes and COPD. This practice may not be justified as our analysis showed that patients with these co-morbidities derived the same benefit from cisplatin administration as their counterparts. Deviations were also more common in low-volume centers. This finding may imply that centers with lesser experience in treating UTC are less aggressive with cisplatin utilization.

Cisplatin administration was associated with OS benefit. An inherent bias exists in this analysis due to distinct patient profiles of better PS and fewer distant metastases in the cisplatin group. To overcome these imbalances, we used multivariate analyses, which showed that this benefit was independent of other prognostic factors. The OS benefit was more pronounced in the eligible-for-cisplatin population, suggesting that this feature is an important factor associated with benefit from cisplatin-based chemotherapy. This notion is strengthened by the finding that outcome of eligible patients was not better than that of ineligible patients when cisplatin was not used. Eligible patients treated with cisplatin had a median OS of 19.4 months, which compares favorably with those reported in randomized trials.16-20 In contrast, eligible patients not treated with cisplatin had a median OS of 12 months. This clinically meaningful difference underlines the importance of adhering to Galsky’s criteria in order to ensure optimal outcome. It is, therefore, important to promptly identify and correct potentially reversible causes of ineligibility, such as recently established renal impairment due to urinary tract obstruction by primary tumor.

Optimal therapy for cisplatin-ineligible patients suffering from aUTC remains an unmet medical need. Importantly, cisplatin was used in 38% of ineligible patients but this was not associated with an equally favorable effect as among eligible patients, which implies that cisplatin-ineligibility may be a surrogate for a more aggressive tumor behavior and not merely unfitness for this particular agent. Currently, carboplatin-based chemotherapy is considered the standard for ineligible-for-cisplatin patients.21 Our results support this recommendation, since carboplatin-based chemotherapy produced a longer median OS than non-platinum therapy. Nevertheless, the median OS of 9.5 months emphasizes the need for developing more effective choices for this population. In this context, the median OS of 15.9 months recently reported for the programmed-death-ligand 1 (PD-L1) inhibitor atezolizumab in 1st-line treatment of ineligible-for-cisplatin patients appears particularly promising.14

The findings of this study set clear targets to improve our management of advanced UTC. Strong emphasis on the eligibility criteria should be considered by Urology and Oncology Scientific and Professional Societies as well as academic institutions and health care providers at national and international level. Referral to centers with experience in treating UTC will improve utilization of cisplatin-based chemotherapy. It should be noted that patients included in this analysis were treated prior to the publication of Galsky et al (2011). It could be speculated that adherence to eligibility criteria has been improved since. Nevertheless, recent observational studies suggested that considerable deviations still exist in everyday practice.[10](#_ENREF_9)

**Conclusions**

All efforts should be made to treat eligible-for-cisplatin patients with aUTC with cisplatin-based chemotherapy to achieve the best possible outcome. The field should recognize that cisplatin may be underutilized and that adherence to published criteria can help increase appropriate cisplatin use. Novel, more effective therapies for ineligible-for-cisplatin patients should be sought through clinical trials specifically focused in this population.

**Tables**

Table 1. Baseline characteristics of 1426 patients according to the type of 1st-line chemotherapy.1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristic | Cisplatin | Carboplatin | Other | P value |
|  | Median, range | | |  |
| Age (n=1411) | 65.1, 34-87 | 71, 38.8-92.9 | 68.4, 34-92 | <0.001 |
| Creatinine clearance (n=990) | 72.6, 20.2-486.2 | 50.5, 1.6-334.6 | 54, 8.6-164.8 | <0.001 |
|  | N (%) | | |  |
| Gender (n=1417)  M  F | 583 (81.5)  132 (18.5) | 325 (76.1)  102 (23.9) | 208 (75.6)  67 (24.4) | 0.035 |
| Neoadjuvant chemotherapy (n=1343)  Yes  No | 47 (6.8)  639 (93.2) | 44 (11.4)  343 (88.6) | 88 (32.6)  182 (67.4) | <0.001 |
| Charlson Comorbidity Index (n=1345)  0  1-2  >2 | 388 (55.9)  190 (27.4)  116 (16.7) | 169 (42.3)  103 (25.7)  128 (32) | 89 (35.5)  94 (37.4)  68 (27.1) | <0.001 |
| Primary site (n=1399)  Bladder  Other | 591 (83.2)  119 (16.8) | 334 (80.1)  83 (19.9) | 223 (82)  49 (18.) | 0.414 |
| Histology (n=1411)  Urothelial  Mixed  Other | 640 (89.5)  46 (6.4)  29 (4.1) | 371 (88.1)  31 (7.4)  19 (4.5) | 229 (83.3)  28 (10.2)  18 (6.5) | 0.121 |
| ECOG PS (n=1107)  0  1  2  3  4 | 257 (44.5)  268 (46.5)  44 (7.6)  7 (1.2)  1 (0.2) | 70 (21.4)  160 (48.9)  80 (24.5)  14 (4.3)  3 (0.9) | 49 (24.1)  110 (54.2)  36 (17.7)  8 (3.9)  0 (0) | <0.001 |
| Center  High-volume (n>100)  Low-volume (n<=100) | 276 (38.2)  446 (61.8) | 140 (32.7)  288 (67.3) | 49 (17.8)  227 (82.2) | <0.001 |
| Metastatic sites (n=1426)  Locoregional  Lymph nodes  Bone  Lung  Liver  Brain  Adrenal  Peritoneum  Distant | 136 (18.9)  451 (62.5)  159 (22)  188 (26)  130 (18)  15 (2.1)  18 (2.5)  19 (2.6)  384 (53.2) | 80 (18.7)  263 (61.5)  131 (30.6)  113 (26.4)  78 (18.2)  7 (1.6)  15 (3.5)  22 (5.1)  258 (60.3) | 51 (18.5)  161 (58.3)  78 (28.3)  80 (29)  44 (15.9)  3 (1.1)  9 (3.3)  20 (7.3)  176 (63.8) | 0.991  0.487  0.003  0.632  0.7  0.552  0.582  0.003  0.004 |
| Risk stratification (n=1107)  Low  Intermediate  High | 257 (44.5)  283 (49.1)  37 (6.4) | 96 (29.4)  164 (50.1)  67 (20.5) | 54 (26.6)  119 (58.6)  30 (14.8) | <0.001 |
|  | | | | |
| Chemotherapy group | n (%) | cycles | |  |
| Median | Range |
| Cisplatin-based  Carboplatin-based  Other | 722 (50.6)  428 (30)  276 (19.4) | 5  4  4 | 1-35  0-21  1-26 |  |

1: When missing values occurred, the number of patients are shown in brackets.

Distant metastases: metastases outside primary site and lymph nodes; Risk stratification: according to the Memorial Sloan Kettering Cancer Center [ref 8]

Table 2. Distribution of eligible-for-cisplatin patients across different treatment groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Eligible-for-cisplatin | N (%) | | | |
| Therapy group | | | Total |
| Cisplatin | Carboplatin | Other |  |
| Yes | 301 (62) | 63 (21) | 64 (32) | 428 (43) |
| No | 186 (38) | 237 (79) | 135 (68) | 558 (57) |
| Total | 487 (100) | 300 (100) | 199 (100) | 986 (100) |

Table 3. Unadjusted hazard ratios and 95% confidence for death in patients who received the first-line chemotherapy1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | n | Median OS (95% CI) | HR (95% CI) | P |
| All patients | 1361 | 14.8 (13.8-15.6) |  |  |
|  |  |  |  |  |
| Therapy group  Cisplatin  Carboplatin  Other | 689  404  268 | 16.7 (14.8-18.5)  10.5 (9.3-11.7)  9.8 (7.9-11.8) | 1  1.71 (1.47-1.97)  1.75 (1.47-2.09) | <.001 |
| Eligible-for-cisplatin  Yes  No  MSKCC risk stratification  Low  Intermediate  High | 550  421  400  554  131 | 15.9 (14.1-18.8)  9.8 (8.6-10.9)  18.7 (15-21.5)  12 (10.9-13.1)  5.4 (4-6.8) | 1  1.73 (1.48-2.02)  1  1.56 (1.33-1.83)  3.8 (3.01-4.79) | <.001  <.001 |
| Eligible-for-cisplatin  Cisplatin-treated  Non-cisplatin-treated  Ineligible-for-cisplatin  Cisplatin-treated  Non-cisplatin-treated  Low risk  Cisplatin-treated  Non-cisplatin-treated  Intermediate risk  Cisplatin-treated  Non-cisplatin-treated  High risk  Cisplatin-treated  Non-cisplatin-treated | 295  126  182  368  251  149  275  279  36  95 | 19.4 (15.9-22.4)  12 (9.5-14.1)  12 (10.8-14.3)  8.6 (7.3-9.7)  22.9 (20.2-26.9)  13.3 (10.7-14.6)  14.3 (12.2-16.2)  10.3 (8.4-11.5)  5.1 (3.8-6.8)  5.8 (3.7-9.3) | 1  2.05 (1.59-2.64)  1  1.36 (1.1-1.69)  1  1.9 (1.47-2.45)  1  1.57 (1.29-1.91)  1  1.04 (0.67-1.6) | <0.001  0.005  <.001  <.001  .870 |

1: Number of patients with survival data in the respective groups are shown in brackets.

OS: overall survival; HR: hazard ratio; CI: confidence interval; MSKCC: Memorial Sloan Kettering Cancer Center;

Table 4. Multivariate analysis for overall survival in patients who received 1st-line chemotherapy

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Factor | | | Subgroups | | HR | | 95% CI | | p-value |
| *Eligibility for cisplatin in Cox regression model (n=738)* | WBC | | | <10000  >10000 | | 1  1.62 | | 1.33-1.97 | | <0.001 |
| PLT | | | <450000  >450000 | | 1  1.36 | | 1.05-1.75 | | 0.020 |
| Distant metastases | | | No  Yes | | 1  1.4 | | 1.17-1.68 | | <0.001 |
| Smoking history | | | Former/Never smoker  Current smoker | | 1  1.24 | | 1.02-1.51 | | 0.033 |
| Eligible for cisplatin | | | Yes  No | | 1  1.56 | | 1.31-1.87 | | <0.001 |
|  | |  |  | |  | |  | |  | |
| *Treatment group in Cox regression model (n=750)* | MSKCC risk | | | Low  Intermediate  High | | 1  1.44  2.281 | | 1.19-1.74  1.69-3.08 | | <0.001 |
| WBC | | | <10000  >10000 | | 1  1.5 | | 1.23-1.81 | | <0.001 |
| Hb | | | >LLN  <LLN | | 1  1.36 | | 1.12-1.66 | | 0.002 |
| Treatment | | | Cisplatin  Non Cisplatin | | 1  1.43 | | 1.19-1.71 | | <0.001 |

HR: hazard ratio; CI: confidence interval; WBC: white blood cells; PLT: platelets; MSKCC: Memorial Sloan Kettering Cancer Center; LLN: Lower limit of normal

**References**

1. Sonpavde G, Watson D, Tourtellott M, et al: Administration of cisplatin-based chemotherapy for advanced urothelial carcinoma in the community. Clin Genitourin Cancer 10:1-5, 2012

2. Dash A, Galsky MD, Vickers AJ, et al: Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer 107:506-13, 2006

3. Linardou H, Aravantinos G, Efstathiou E, et al: Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: Phase II study of the Hellenic Co-operative Oncology Group. Urology 64:479-84, 2004

4. Bamias A, Lainakis G, Kastritis E, et al: Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. Oncology 73:290-7, 2007

5. Bellmunt J, de Wit R, Albanell J, et al: A feasibility study of carboplatin with fixed dose of gemcitabine in "unfit" patients with advanced bladder cancer. Eur J Cancer 37:2212-5, 2001

6. Carles J, Nogue M, Domenech M, et al: Carboplatin-gemcitabine treatment of patients with transitional cell carcinoma of the bladder and impaired renal function. Oncology 59:24-7, 2000

7. De Santis M, Bellmunt J, Mead G, et al: Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. J Clin Oncol 27:5634-9, 2009

8. Bajorin DF, Dodd PM, Mazumdar M, et al: Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 17:3173-81, 1999

9. Galsky MD, Hahn NM, Rosenberg J, et al: Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol 29:2432-8, 2011

10. Bamias A, Peroukidis S, Stamatopoulou S, et al: Utilization of Systemic Chemotherapy in Advanced Urothelial Cancer: A Retrospective Collaborative Study by the Hellenic Genitourinary Cancer Group (HGUCG). Clin Genitourin Cancer 14:e153-9, 2016

11. Necchi A, Sonpavde G, Lo Vullo S, et al; RISC Investigators. Nomogram-based Prediction of Overall Survival in Patients with Metastatic Urothelial Carcinoma Receiving First-line Platinum-based Chemotherapy: Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Eur Urol. doi: 10.1016/j.eururo.2016.09.042, 2016

12. Ramos JD, Casey MF, Bamias A, et al; Retrospective International Study of Cancers of the Urothelium (RISC) Investigators. The Khorana Score in Predicting Venous Thromboembolism for Patients With Metastatic Urothelial Carcinoma and Variant Histology Treated With Chemotherapy. Clin Appl Thromb Hemost. pii: 1076029616668405, 2016

13. Ramos JD, Casey MF, Crabb SJ, et al; RISC Investigators. Venous thromboembolism in metastatic urothelial carcinoma or variant histologies: incidence, associative factors, and effect on survival. Cancer Med. doi: 10.1002/cam4.986, 2016

14. Bellmunt J, Balar A, Galsky MD, et al: IMvigor210: updated analyses of first-line (1L) atezolizumab (atezo) in cisplatin (cis)-ineligible locally advanced/metastatic urothelial carcinoma (mUC). Annals of Oncology 27, 2016

15. Balar A, Bellmunt J, O'Donnell PH, et al: Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: Preliminary results from the phase 2 KEYNOTE-052 study. Annals of Oncology 27, 2016

16. Sternberg CN, de Mulder PH, Schornagel JH, et al: Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 19:2638-46, 2001

17. von der Maase H, Hansen SW, Roberts JT, et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 18:3068-77, 2000

18. Bamias A, Aravantinos G, Deliveliotis C, et al: Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol 22:220-8, 2004

19. Bamias A, Dafni U, Karadimou A, et al: Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol 24:1011-7, 2013

20. Bellmunt J, von der Maase H, Mead GM, et al: Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 30:1107-13, 2012

21. Bellmunt J, Orsola A, Leow JJ, et al: Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 25:iii40-iii48, 2014

**Figure legends**

Figure 1. Study flow chart

Figure 2. Kaplan-Meier curves of overall survival according to: the type of 1st-line chemotherapy (a); eligibility-for-cisplatin (b); the type of 1st-line chemotherapy among eligible-for-cisplatin patients (c); the type of 1st-line chemotherapy among ineligible-for-cisplatin patients (d); eligibility-for-cisplatin stratified by cisplatin utilization (e); the Memorial Sloan Kettering Cancer Center risk group (ref 8) stratified by cisplatin utilization (f). Maximum analysis time to be graphed was selected at 5 to 6 years. Patients alive at 5-6 years (regardless of subsequent death) were censored at that time; (g) Forest plot of subgroup analysis according to the type of 1st-line chemotherapy. Blue dots denote hazard ratios for the treatment type and horizontal bars 95% confidence interval. Interaction refers to potential interactions of the effects of treatment type (cisplatin vs. carboplatin+other) and each of the covariates listed on the left-hand side of the figure. P-value of interaction refers to the p-value of the interaction term from a Cox model, which includes treatment type and the respective covariate. CCI: Charlson Comorbidity Index; COPD: chronic obstructive airway disease; PS: performance status; Hgb: hemoglobin; WBC: while blood cells. Risk groups according to the Memorial Sloan Kettering Cancer Center (ref 8)