Review Article

Second Line Chemotherapy for Advanced and Metastatic Urothelial Carcinoma: Vinflunine and Beyond—A Comprehensive Review of the Current Literature

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Abbreviations and Acronyms

BSC = best supportive care
CR = complete response
EGFR = epidermal growth factor receptor
GC = gemcitabine and cisplatin
Her = human epidermal growth factor receptor
MTX = methotrexate
MVAC = methotrexate, vinblastine, doxorubicin and cisplatin
ORR = objective response rate
OS = overall survival
PD = programmed death
PD-L1 = PD-ligand 1
PFS = progression-free survival
PS = performance status
TKI = tyrosine kinase inhibitor
TTP = time to progression
UC = urothelial carcinoma
UCB = bladder UC
VEGF = vascular endothelial growth factor
VEGFR = VEGF receptor

Purpose: We comprehensively reviewed current efforts and advances in the field of chemotherapeutic and biologically targeted treatment options after the failure of cisplatin based, first line regimens for urothelial carcinoma.

Materials and Methods: We searched MEDLINE®, Central®, and meeting abstracts of ASCO (American Society of Clinical Oncology) and ESMO (European Society for Medical Oncology) to identify original articles, reviews and retrospective analyses on second line treatment of urothelial carcinoma. Articles were included in analysis if they described prospective phase II/III studies or larger high quality retrospective studies of second line treatment of urothelial carcinoma.

Results: Although considered a chemosensitive disease, most patients with advanced or metastatic urothelial carcinoma relapse after cisplatin based first line treatment. Today none of the commonly used drugs, ie paclitaxel, carboplatin and/or gemcitabine, are approved by the FDA (Food and Drug Administration) for second line systemic treatment. In Europe vinflunine plus best supportive care is the only option approved by the EMA (European Medicines Agency) with moderate clinical efficacy. Responses to combined chemotherapy approaches are often better but associated with remarkable toxicity. In patients who respond well to first line treatment and, thus, are considered cisplatin sensitive readministration of a platinum based combination regimen may be an option. To date targeted therapies do not have a role in second line treatment of urothelial cancer. Immunotherapeutic strategies to target the PD-1/PD-L1 axis are emerging. In a recent phase I trial evaluating the PD-L1 targeted monoclonal antibody MPDL3280A a promising 43% response rate with good tolerability was achieved, which led to an immediate breakthrough therapy designation by the FDA. Combining chemotherapy with targeted agents, eg weekly paclitaxel and pazopanib, also shows promising activity in this prognostically poor treatment situation.

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Conclusions: Response rates and survival are poor after second line chemotherapy for advanced or metastatic urothelial carcinoma. To improve outcomes of salvage treatment novel biologically targeted drugs as monotherapy or as part of a combination with conventional cytostatics are urgently needed.

Key Words: urinary bladder, urothelium, carcinoma, drug therapy, salvage therapy

UROTHELIAL carcinoma of the bladder is considered a chemosensitive disease. Systemic chemotherapy is considered the treatment of choice in patients with advanced and/or metastatic UC. Only few randomized clinical trials have been performed in the first line setting and even fewer in the second line setting for advanced or metastatic UC.[1] Despite the response rates of 40% to 60% achieved by cisplatin based first line chemotherapy (eg GC, MVAC or dose dense MVAC) most cases progress at a median of about 8 months and optimal subsequent systemic treatment remains unsettled.

Second line single agents have only shown marginal activity after the failure of cisplatin based treatment with an ORR of 5% to 20% and a median PFS of only 3 to 4 months. Moreover there is hardly any evidence that second line systemic treatment may substantially improve OS or quality of life.[2] Importantly none of the currently used drugs have been approved by the United States FDA in this setting. However, in accordance with the current NCCN Guidelines® for Bladder Cancer, version 1.2015, taxanes and/or gemcitabine are commonly used for palliation based on the modest response rates in several small, nonrandomized phase II trials. In 2009 EMA approved vinflunine as a second line therapeutic option in this setting.

Generally patient impaired renal function, poor PS, advanced age and comorbidities have limited trial design, feasibility and patient accrual, particularly in the second line setting.[1] These factors result in less benefit from chemotherapy and unfavorable side effect profiles. Therefore, BSC remains the most feasible approach in this situation for most patients. Furthermore, comparisons of trial results are fundamentally limited for several reasons. The lack of a generally accepted definition of second line chemotherapy (ie patients who had received perioperative chemotherapy or first line treatment for metastatic disease), different localizations of the primary tumor (ie UCB or upper tract UC) and missing stratification into risk groups by established prognostic parameters (eg the Bajorin criteria) subsequently result in highly heterogeneous study populations.

The objective of this review was to provide an updated, comprehensive overview of the progress made to define valuable second line treatment options for advanced and/or metastatic UC in the last 3 decades, including results from emerging developments in targeted therapy approaches.

MATERIALS AND METHODS

We performed a comprehensive literature search of MEDLINE/PubMed®, Central, ClinicalTrials.gov, the ASCO meeting library and ESMO annual meeting abstracts until April 2015 to identify original articles on prospective studies, retrospective analyses, review articles, editorials and ongoing studies regarding second line treatment of UC. Single case reports were excluded from analysis. Searches were limited to the English language and human adults with UC. MeSH® term key words with several sets of combinations were applied to identify appropriate publications, including urothelial carcinoma or cancer, transitional cell carcinoma, urinary bladder cancer or neoplasms, upper urinary tract, second-line, salvage, chemotherapy, cisplatin-refractory and cisplatin-resistant.

All abstracts were reviewed by 2 of us (CO and MR) and the corresponding full-length articles of those most relevant to each subsection were analyzed. Studies of additional interest referenced in originally retrieved full-length articles were located by selective search and reviewed. Except for 3 randomized, controlled trials the included articles described nonrandomized, single arm phase II trials, 3 phase I studies and 7 retrospective analyses. Due to the high population heterogeneity regarding patient and disease related factors (eg localization of primary UC, perioperative vs first line intent and number of treatment lines prior to the reported systemic treatment) no comparative analysis was performed.

RESULTS

Active Single Agents

In the United States no second line treatment is approved by the FDA but in accordance with current NCCN Guidelines taxanes and/or gemcitabine is often used for palliation. In Europe vinflunine is the only EMA approved second line chemotherapy agent for metastatic UC after cisplatin based first line treatment based on the results of a randomized phase III trial.[3] Trials comparing other agents to vinflunine in a randomized approach are lacking.

Numerous phase II studies have investigated single agent chemotherapy. Response rates were rather low (0% to 29%) and only short median PFS and OS were achieved. The gain of cancer specific survival under second line chemotherapy vs BSC