Salvage Systemic Therapy for Advanced Urothelial Carcinoma: On the Cusp of a Sea Change?

GURU SONPAVDE, a JOAQUIM BELLMUNT b

aUniversity of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, Alabama, USA; bDana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Advanced urothelial cancer • Salvage therapy

CURRENT SYSTEMIC THERAPY FOR ADVANCED UROTHELIAL CARCINOMA

First-line cisplatin-based combination chemotherapy yields a median overall survival (OS) of 12–15 months in advanced urothelial carcinoma (UC) and is associated with durable survival in a fraction of patients with excellent performance status and no visceral disease. There are currently no agents approved by the U.S. Food and Drug Administration for the second-line systemic therapy of advanced UC. Vinflunine is approved in Europe based on a phase III trial that demonstrated extension of OS compared with best supportive care in a predefined eligible population and yielded a median progression-free survival (PFS) and OS of 3 and 6.9 months, respectively [1]. These outcomes with vinflunine appear similar to taxanes, which are commonly used in the U.S. as second-line therapy based on activity in phase II trials [2].

IS PEMETREXED A REASONABLE SALVAGE CHEMOTHERAPY OPTION IN ADVANCED UC?

Pemetrexed, a folate antimetabolite, appeared to demonstrate modest activity in one phase II trial that led to the incorporation of pemetrexed as a reasonable second-line agent by the National Comprehensive Cancer Center Network guidelines [3]. In this trial, 45 evaluable patients were enrolled, of whom 3 (6.4%) exhibited complete responses and 10 (21.3%) exhibited partial responses (PR) for an overall response rate (ORR) of 27.7%. The median PFS was 2.9 months, and median OS was 9.6 months. Responses were generally seen in patients receiving prior perioperative chemotherapy. However, among those with platinum-refractory disease progressing on or within 1 month of platinum-based therapy, the median survival was only 4.4 months. In contrast, another phase II trial of second-line pemetrexed closed early for lack of the minimal threshold of response required [4]. The large retrospective study of pemetrexed (n = 129) as salvage systemic therapy reported in this issue of The Oncologist by Bambury et al. [5] provides more convincing data, suggesting its limited activity in an unselected population. In this data set, the ORR, median PFS, and median OS were 5%, 2.4 months, and 6.7 months, respectively.

USE OF VALIDATED NOMOGRAM TO INTERPRET ACTIVITY OF SALVAGE AGENTS IN NONRANDOMIZED STUDIES

An externally validated nomogram uses the four major prognostic factors (performance status [PS], hemoglobin [Hb], liver metastasis, and time from prior therapy) to assist in interpreting the PFS at 6 months (PFS6) of agents in nonrandomized phase II studies enrolling heterogeneous populations [6, 7]. Because this nomogram was constructed using a taxane-dominated data set, it essentially calculates the expected probability of PFS6 at the individual patient level when using a taxane and allows its indirect comparison with observed activity when evaluating a new agent. PFS6 was previously demonstrated to be robustly associated with OS compared with response as an intermediate surrogate for OS [8]. In the retrospective study by Bambury et al. [5], the observed PFS6 of 14% did not appear longer than the predicted PFS6 of 17% [9]. This disappointing activity of pemetrexed in unselected patients should relegate pemetrexed to a potential salvage option only if clinical trials are unavailable. Potentially, the discovery of predictive biomarkers may help select patients likely to derive durable benefits and provide a well-defined role for pemetrexed.

CLINICAL TRIALS ARE THE STANDARD OF CARE FOR SECOND-LINE OR LATER-LINE SYSTEMIC THERAPY

Multiple clinical trials are evaluating novel and promising agents, which should be generally preferred as salvage therapy (Table 1). Notably, programmed death 1 (PD-1) inhibitors and PD ligand 1 (PD-L1) inhibitors appear highly promising, and responses have been durable in most patients, although the global PFS is still poor [10]. To add to the excitement surrounding PD-1 and PD-L1 inhibitors, there is the promise of developing a predictive biomarker—various thresholds using different assays suggest that higher tumor cell and/or stromal expression of PD-L1 protein has been associated with a higher probability of response, which offers the promise of

Correspondence: Guru Sonpavde, M.D., University of Alabama at Birmingham Comprehensive Cancer Center, 1720 2nd Avenue South, NP2540B, Birmingham, Alabama 35294, USA. Telephone: 205-975-3742; E-Mail: gsonpavde@uabmc.edu Received March 1, 2015; accepted for publication March 13, 2015; published Online First on April 6, 2015. ©AlphaMed Press 1083-7159/2015/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2015-0077

developing precision medicine when using this class of immunotherapeutic agents. Additionally, tubulin targeting chemotherapeutic agents (e.g., nanoparticle albumin-bound paclitaxel, eribulin), vascular endothelial growth factor receptor inhibitors (pazopanib, cabozantinib, ramucirumab), and fibroblast growth factor receptor (FGFR)-3 inhibitors may confer an incremental benefit at least in a subset of patients [11–15]. Preliminarily, cabozantinib decreased regulatory T lymphocytes (Tregs) and increased PD-1 expression in Tregs, suggesting potential synergism with PD-1 inhibitors.

**THE VALUE OF IMPROVED PROGNOSTIC CLASSIFICATION**

Optimal information regarding prognostic factors can help risk-stratify patients, tailor monitoring strategies, and interpret and design clinical trials. The study by Bambury et al. [5] also examined prognostic factors and suggests a prognostic impact for the neutrophil-lymphocyte ratio (NLR), which has been shown to be prognostic across malignancies [16]. More recently, a retrospective analysis of prospective trials externally validated the independent prognostic impact of hypoalbuminemia after controlling for the four recognized factors [17]. However, neutrophil and platelet counts, as well as NLR, could not be externally validated in this study. Thus, this five-factor salvage prognostic model (PS, Hb, liver metastasis, time from prior therapy, and hypoalbuminemia) resembles the four-factor first-line prognostic model, which includes anemia, PS, hypoalbuminemia, and visceral metastasis [18]. Molecular prognostic factors are not validated or ready for clinical trial designs. The comprehensive tumor tissue genomic analyses by the Cancer Genome Atlas suggest substantial genomic heterogeneity, a large mutation burden, and no single dominant alteration but potential therapeutic targets in 69% of tumors, including targets in the EGFR/HER2/HER3, phosphatidylinositol 3-kinase/AKT/mTOR, and mitogen-activated protein kinase pathways [20]. The role for targeting FGFR3 is being elucidated given the prevalence of FGFR3 mutations and translocations in a subset of advanced UC. Interestingly, chromatin-regulated genes were frequently mutated compared with other malignancies, suggesting a potential role for epigenetic modulation.

Consequently, trials enrolling unselected patients may have a poor chance of demonstrating benefit. Thus, umbrella trials matching patients with suitable agents should be strongly considered. Indeed, one such umbrella trial (MATCH UP trial) is being planned through the U.S. cooperative group mechanism to assign patients to agents based on alterations. However, all agents on this trial are being provided by a single pharmaceutical company, given the challenges of collaborating with multiple companies with differing priorities (which limits the range of agents that can be investigated). In addition, combinations of biologic agents may yield larger increments and warrant aggressive preclinical and clinical investigation. Conversely, the large mutation burden in UC might explain the preliminary role for immunotherapy in a broad population, which may be hypothesized to be more active against tumors harboring more neoantigens [10].
Although new agents have almost exclusively been evaluated in first- and second-line settings, other settings deserve greater attention. Given the potentially greater role for immunotherapy in the microscopic disease setting, vigorous phase III evaluation of PD-1 and PD-L1 inhibitors is planned as adjuvant therapy for muscle-invasive bladder cancer. The neoadjuvant therapy paradigm should also be exploited to detect a signal of biologic and antitumor activity. However, the caveat is that the magnitude of biologic activity with brief neoadjuvant therapy that will translate to improved long-term outcomes with prolonged therapy for metastatic disease is unclear and is probably different between classes of agents. Combinations and alternate sequences of cisplatin-based chemotherapy and biologic agents may be assessed as neoadjuvant therapy to identify an increment in pathologic complete remission. Finally, switch maintenance to a tolerable biologic agent in those with at least stable disease following first-line chemotherapy warrants serious consideration because progression is almost inevitable, and the majority of patients may be unfit for second-line chemotherapy at the time of progression.

**Better Interdisciplinary Collaboration Is Critical**

Finally, the urologic oncology community should collaborate better to make rapid advances. Historically, the interface between medical oncologists and urologists has been challenging at best and difficult at worst. As an example, the pivotal phase III trial conducted by the Southwest Oncology Group evaluating neoadjuvant cisplatin-based chemotherapy took 11 years to accrue 317 patients and thereafter has been followed by slow or no uptake by many urologists even today, more than a decade after its publication. Needless to say, the academic community needs to collaborate and have a shared consensus vision for the future development of therapy. It is reassuring that recent trends indicate increasing referrals for neoadjuvant chemotherapy.

**REFERENCES**


**Author Contributions**

Conception/Design: Guru Sonpavde

Provision of study material or patients: Guru Sonpavde, Joaquim Bellmunt

Collection and/or assembly of data: Guru Sonpavde, Joaquim Bellmunt

Data analysis and interpretation: Guru Sonpavde, Joaquim Bellmunt

Manuscript writing: Guru Sonpavde, Joaquim Bellmunt

Final approval of manuscript: Guru Sonpavde, Joaquim Bellmunt

**DISCLOSURES**

Guru Sonpavde: Merck, Genentech, Sanofi, Bayer (C/A, SAB), Onyx (RF); Joaquim Bellmunt: Pierre Fabre, Astellas, Pfizer, Merck (C/A), Takeda, Sanofi (RF).

(C/A) Consulting/Advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (O) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

**EDITOR’S NOTE:** See the related article, “The Safety and Efficacy of Single-Agent Pemetrexed in Platinum-Resistant Advanced Urothelial Carcinoma: A Large Single-Institution Experience,” by Richard M. Bambury et al., on page 508 of this issue.