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Paper Alert

Beyond Cisplatin – I

Edward M. Messing*
University of Rochester Medical Center, Rochester, NY, USA

Roughly 25% of patients at diagnosis of urothelial cancer (UC) have at least muscle invasive disease [1] and about half of these have extravesical extension or more advanced disease at that time. Additionally 10–15% of patients who initially have non-muscle invasive UC will subsequently develop muscle invasive or more advanced cancer. The outlook for patients with advanced or metastatic UC, particularly those who do not respond to Cisplatin-based combination chemotherapy regimens is very poor. Moreover, except in adjuvant and neoadjuvant settings, despite objective response rates to Cisplatin based combination therapies of about 50% [2] median survival is only about 15 months and time to progression far briefer, with 5 year survival only being about 15% [3]. Additionally, because of comorbidities and frailty, many patients with advanced UC cannot receive these Cisplatin containing regimens. Relapsing patients respond poorly to additional treatments with median survival of usually <10 months [4]. However two "new" approaches have appeared on the horizon to treat such patients which take advantage of great advances in molecular biology over the past 15 years which give some reason for optimism. The first is targeted molecular therapies which are tied to our increased understanding of urothelial cancer's molecular and genetic makeup (as illustrated by The Cancer Genome Atlas [TCGA]) [5], and the second, is the emergence of immune checkpoint inhibitors as viable options for systemic treatment of UC. We will focus on the former in this Paper Alert, and will review new articles on the immune modulators in a later edition.

It should be noted that the TCGA and numerous other studies have shown urothelial cancer to be a molecularly diverse disease with modifications of the PI3 kinase- AKT- PTEN- mTOR pathway, the epidermal growth factor (EGF) family of growth factor receptors, fibroblast growth factor receptor-3 (FGFR3), and various vascular endothelial growth factor receptors (VEGFRs). One or more of these "targets" are abnormal in 15–50% of advanced urothelial cancer specimens.

However, the definition of what is "abnormal" (e.g. mutations, overexpression, gene amplification, etc.) is not standardized to remotely the degree that a clinical test should be, so failure to predict response to targeted agents is not surprising. This is discussed in a "Special Article" in the Journal of Clinical Oncology [6], which details attempts by the National Cancer Institute (NCI), the Food and Drug Administration (FDA), various cancer organizations such as the American Society of Clinical Oncology (ASCO), and the American Association of Cancer Research (AACR) to improve standardization, while understanding the urgent need our patients have. As is almost always the case, especially with how costly targeted agents are, the Center for Medicare and Medicaid will have to wield an important "hammer" to assist this process.

But beyond standardization of tests are numerous other issues which are practical hurdles to making "personalized medicine" a reality for patients with advanced UC. These are outlined by Plimack and Geynisman [7]. Perhaps the most concerning is the realization that even if tissue is obtained

*Correspondence to: Edward M. Messing, University of Rochester Medical Center, Rochester, NY, USA. Tel.: +1 585 275 3345; E-mail: Edward.messing@urmc.rochester.edu.

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for biomarker discovery, the practical aspects of biopsying tissue, sending it for molecular analysis, and receiving results concerning "actionable" molecular targets was reported by Sohal et al. [8] to take 25 days with results being uninformative or unevaluable in over half the patients and only 22% receiving molecularly driven targeted therapies [8]. That fewer than 10% of those treated had objective responses in a highly motivated institution (The Cleveland Clinic) attests to the logistical problems of bringing this technology to the clinic. Among serious issues were disease progression during this time and getting access to drugs, either through available clinical trials or commercial insurer approval.

A second matter that Plimack and Geynisman point out is that given all of the genetic changes that occur in advanced UC, deciding on "molecular drivers" of malignant behavior is not only complex, but is made far more difficult because often the only tissue available is from primary tumors harvested months or years before, which may not express the important molecular changes in metastases, particularly in those cancers that have survived and progressed while patients have been receiving chemotherapy. This further extends the waiting period between tissue procurement and receiving the "correct" targeted treatments.

However, all is not gloom [7]. Cheetham and Petrylak [9] point out that particularly the anti-VEGF antibody, Bevacizumab, in combination with Gemcitabine-Carboplatin in a phase II study of chemotherapy naïve, cisplatin ineligible patients with advanced UC showed response rates of nearly 50% and median survivals of nearly 14 months, and the VEGFR2 inhibitor [10]. Ramucirumab given with docetaxel achieved response rates of nearly 25% and median survivals of >10 months in patients heavily pretreated with cisplatin chemotherapy [11]. Moreover, neither of these studies used biomarkers to select participants; since if they had, a higher proportion of responses may have been seen. Interestingly, in other studies, inhibitors of VEGF-R1 and VEGF-R3 were not effective [7].

In a separate report [12], Afatinib, an oral irreversible inhibitor of the ErbB receptor family was used as a single agent in 23 patients with metastatic UC, and while only 22% (N = 5) of patients had responses, 5 of the 6 patients with HER2 or ErbB3 alterations accounted for all of these, while none of the 15 without either of these alterations responded. Moreover the one patient with both HER2 amplification and ErbB3 mutations achieved the longest response (10.3 months), actually never progressing while on therapy (stopped because of reduced cardiac ejection fraction which may or may not have been related to the drug). While ErbB3 does not have intrinsic receptor tyrosine kinase activity, it is thought to dimerize with HER2, increasing activity of HER2 akin to amplification of HER2. These alterations in HER2 and ErbB3 were determined by genetic analyses, which did not correlate with immunhistochemical (IHC) expression of the proteins – and, as opposed to the genetic analyses, IHC did not correlated with clinical response. Diarrhea, fatigue and rash were major side effects but only 2 patients experienced grade 3 toxicity.

The papers reviewed here illustrate both the promise and complexities of studying targeted agents in advanced UC. While there's much work still to do, we now have begun to have means to help patients who are refractory to, or unsuitable for cisplatin therapy.

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