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Editorial

Neoadjuvant Chemotherapy in the Medical Management of Muscle-Invasive Bladder Cancer

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EDITORIAL

Muscle-invasive bladder cancer (MIBC) is a lethal disease for which cytotoxic, platinum-based chemotherapy remains the standard of care. Recent insights into the genomic landscape of MIBC reveal a highly heterogeneous disease. As a result, targeted therapies have yet to demonstrate significant clinical benefit for the majority of patients. While cisplatin-based neoadjuvant chemotherapy (NAC) has a proven overall survival (OS) benefit for MIBC, use of this treatment has been limited by perceived lack of benefit and risk of toxicity. However, OS is significantly improved for patients who experience a pathologic complete response to NAC. Predictive biomarkers of platinum-sensitivity could have a substantial impact on clinical outcomes for MIBC through the identification of patients most likely to respond to NAC.

Despite significant therapeutic advances in medical oncology over the last decade, neither the standard of care nor the clinical outcomes for patients with muscle-invasive bladder cancer (MIBC) have changed in over 30 years [1]. Approximately 50% of patients with clinically organ-confined MIBC who undergo curative radical cystectomy relapse and die of advanced MIBC. The median overall survival (OS) for patients with advanced MIBC is 14 months. Furthermore, no Food and Drug Administration (FDA) -approved second line therapies exist for patients who have progressed on a first-line platinum-containing chemotherapy regimen. We clearly need to do better for our patients.

Bladder cancer (BC) is increasingly being recognized as an extremely heterogeneous disease. Potentially actionable genomic alterations have been identified in over 60% of BC, and BC is second only to serous ovarian carcinoma in the fraction of the genome that is altered [2]. If the linchpin of precision medicine is matching the right targeted therapy to the right tumor and patient, this large degree of genomic heterogeneity represents a significant hurdle to clinical trial design and enrollment. Recent clinical trials of the targeted agents everolimus and dovitinib in metastatic urothelial carcinoma (UC) illustrate the importance of prospective genomic characterization in order to enrich the study population for the molecular targets of interest [3,4]. For example, the tumor of the only patient who experienced a durable response to everolimus, an inhibitor of the mammalian target of rapamycin (mTOR) pathway, harbored a somatic mutation in tuberous sclerosis complex 1 (*TSC1*), which regulates the activation of the mTOR pathway [3,5]. *TSC1* mutations were subsequently identified in less than 10% of UC tumors, and thus are rare events in an unselected population. Despite promising preclinical activity in UC with *FGFR3*-activating mutations or protein overexpression, the angiogenesis and FGFR3 inhibitor dovitinib (TKI258) was not associated with clinical benefit in patients with advanced UC regardless of *FGFR3* mutation or expression status [4]. Possible explanations for the lack of activity include an incomplete understanding of which genomic alterations render tumors sensitive to disruption of the FGFR3 pathway or lack of specificity of the agent for the purported targets.

While the field awaits further evidence of the role of targeted therapy in MIBC, current medical management of this disease relies upon the use of cytotoxic, combination chemotherapy. Despite being associated with a proven OS benefit for patients with clinically organ-confined MIBC, the use of cisplatin-based neoadjuvant chemotherapy (NAC) is limited in clinical practice due to a number of factors, including a perceived lack of benefit. A meta-analysis of randomized trials of cisplatin-based combination NAC in organ-confined MIBC demonstrated a 5% absolute improvement in OS at 5 years [6]. However, for patients who receive NAC followed by radical cystectomy (RC), the pathologic complete response rate (pCR) is doubled from roughly 10-15% to 28-30%, and the 5 year OS increased from 40-50% to 85% [7]. Concerns over increased perioperative morbidity and mortality or inability to undergo RC following chemotherapy have not been borne out in randomized studies [8,9]. Trials of adjuvant chemotherapy for MIBC are inconclusive, largely due to methodological flaws [10]. Furthermore, more patients are eligible for cisplatin prior to RC rather than after due to prolonged surgical recovery or impaired renal function [11,12]. Thus, NAC is the preferred approach for the management of patients with MIBC who are eligible to receive cisplatin-based chemotherapy, as reflected in the most recent treatment guidelines from the National Comprehensive Cancer Network (NCCN) [13].

Additional benefits of NAC include the potential to render locally advanced tumors resectable and pathologic assessment of tumor response to treatment with immediate implications for long-term prognosis [7]. The neoadjuvant model has also

been viewed as a platform by which to study the activity of novel agents. According to the FDA, pCR is under consideration as an endpoint for accelerated drug approval in breast cancer [14]. This potential paradigm shift could lead to similar options in other malignancies. As new agents with anti-tumor activity are identified in MIBC, neoadjuvant studies of such drugs have the potential to provide early evidence of clinical benefit. To ensure the timely completion of such trials, physicians must be prepared to offer enrollment to their patients. Estimates of the current use of NAC, both in the community and at academic centers, are extremely low [15]. A multidisciplinary approach to care with early referral to medical oncology has been successful in increasing rates of NAC use and was recently proposed as a quality indicator in the management of MIBC [16,17].

Along with greater physician awareness of the benefits of NAC, future research efforts must be directed towards the identification of predictive biomarkers of response to cisplatin-based NAC. In addition to sparing patients who are unlikely to respond the toxicity of treatment, such biomarkers will also provide patient-specific information of the benefit of treatment for individuals. Markers of DNA repair have been investigated for their role in tumor response to platinum-induced DNA damage. For example, reduced excision repair cross-complementing group 1 (ERCC1) protein expression, a key component of the nucleotide excision repair pathway, has been associated with improved OS in patients with MIBC treated with cisplatin-containing NAC [18]. Improved pCR rates following cisplatin-based NAC were observed in patients with reduced mRNA levels of breast cancer susceptibility gene 1 (BRCA1), involved in homologous recombination [19]. Gene expression models have been shown to predict improved OS following cisplatin-containing NAC for MIBC, and this approach is being prospectively evaluated in a clinical trial of different NAC regimens sponsored by the Southwest Oncology Group [20]. Efforts such as these will lead the way to identification of predictive biomarkers that ultimately could improve care for all patients with MIBC by ensuring that those most likely to benefit from NAC receive appropriate therapy.

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