Targeting Angiogenesis in Bladder Cancer

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Introduction
Bladder cancer is the fourth most common cancer and the ninth leading cause of cancer death in the United States [1]. It is estimated that in 2008, there were about 68,810 new cases of bladder cancer diagnosed in the United States and 14,100 deaths (~9950 in men and 4150 in women); the vast majority of cases were transitional cell carcinoma (TCC). More than 70% of the incidence is the result of papillary noninvasive tumors that may recur in most patients but only infrequently progress to invasive disease. Most deaths due to TCC are related to the 20% to 30% of cases of nonpapillary invasive or metastatic TCC. These tumors can penetrate deeply through the bladder wall and demonstrate a high propensity for lymphatic and distant metastasis.

Invasive TCC requires aggressive therapy, as many patients are at risk for death due to metastatic disease. Neoadjuvant combination cisplatin-based chemotherapy followed by radical cystectomy offers a modest improvement in survival in patients with invasive TCC [2]. There may be a similar benefit with adjuvant chemotherapy, but this remains unproven [3]. In metastatic TCC, the responses to chemotherapy are frequent but not durable. Gemcitabine/cisplatin (GC), the most commonly used first-line chemotherapy regimen in TCC, has largely replaced MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) as the standard of care on the basis of an international phase 3 trial showing similar overall survival with significantly less toxicity [4]. Updated results from this trial demonstrated a median time to progression (TTP) of 7.7 months and median overall survival of 14.0 months for patients treated with GC [5]. However, most patients with metastatic disease cannot be cured by conventional cytotoxic chemotherapy. Further results from this clinical trial continue to affirm similar long-term disease outcomes between these two regimens. Long-term survival in patients with metastatic disease remains poor, with only 12% to 15% alive at 5 years. To improve survival in advanced disease, novel therapies that target the biologic processes related to TCC growth and progression are needed.

Angiogenesis in Bladder Cancer
Angiogenesis is required for tumor growth and metastasis [6,7]. In normal adult tissues, neovascularization is required only for repair of tissue injury. In malignant tissues, neovascularization is required for tumors to grow beyond a certain size and to metastasize to new sites. A fine balance between stimulatory and inhibitory factors produced by the tumor and the surrounding stroma regulates new blood vessel development [8]. Bladder tumors produce high levels of multiple angiogenic stimulatory factors, including vascular endothelial growth factor (VEGF) [9,10], basic fibroblast growth factor (bFGF) [11,12], and interleukin-8 [13]. Levels of these factors correlate with stage and outcome [14,15]. Microvessel density, a surrogate marker for angiogenic activity, is a predictor of disease progression, vascular invasion, lymph node involvement, tumor recurrence, and poor survival in invasive TCC [16–21]. Levels of VEGF and bFGF are inversely associated with prognosis [22]. Based on these findings, it is hypothesized that targeting angiogenesis pathways alone or in combination with standard
chemotherapeutic regimens in TCC of the bladder will lead to improvement in patient outcomes.

VEGF
Preclinical models in bladder cancer suggest that anti-angiogenic therapies may inhibit progression of bladder cancer and that VEGF is the primary proangiogenic mediator of this progression [18,23–25]. VEGF mRNA and protein are overexpressed in advanced bladder cancer compared with normal bladder epithelium [10,26,27]. In addition to VEGF's proangiogenic properties, recent in vitro experiments suggest a role for VEGF signaling as an autocrine and paracrine growth factor to directly promote bladder cancer growth [28]. Furthermore, retrospective evaluation of serum VEGF levels in the metastatic setting appears to correlate high levels with poor disease-free survival [29]. Baseline VEGF mRNA expression levels and microvessel density were found to be independent prognostic factors for recurrence and metastasis in 51 patients treated with neoadjuvant MVAC chemotherapy and cystectomy [30].

In addition to the proangiogenic role of VEGF, elevated levels of this factor in tumors lead to abnormal microvasculature. Excessive angiogenic factors recruit endothelial and perivascular cells to form tortuous and dilated blood vessels with poor rheologic characteristics, leading to abnormal tumor blood flow. Elevated VEGF levels in tumors result in increased vascular permeability [31]. These changes lead to increased interstitial fluid pressure, which impairs the delivery of chemotherapy to tumor cells because of a decrease in the pressure gradient [32–34]. By reducing VEGF levels, not only are the aberrant tumor-associated blood vessels eliminated, but the microvasculature also appears to be remodeled, resulting in more “normal” blood vessel architecture. This leads to improved transvascular drug delivery directly to tumor cells. Anti-VEGF strategies decrease interstitial fluid pressure in tumors and enhance delivery of chemotherapy to tumor cells, resulting in improved and prolonged responses [34]. These strategies have proven beneficial in prolonging overall survival in colorectal and non–small cell lung carcinoma.

Anti-VEGF Therapeutic Strategies
Multiple agents are now available that target angiogenesis and the VEGF pathway. Agents such as bevacizumab, which targets the VEGF ligand, and sunitinib and sorafenib, which target the VEGF receptor (VEGFR), are being tested in advanced TCC.

Bevacizumab in advanced TCC
Based on the evidence that angiogenesis and VEGF play an important role in TCC progression and that TCC is a chemosensitive disease, as well as the preclinical data showing that bevacizumab improves chemotherapy delivery, locally advanced or metastatic TCC represents an opportunity to test anti-VEGF strategies to improve clinical outcomes. Preclinical studies have shown that adding anti-VEGF strategies to TCC chemotherapy leads to improved responses [34–37].

In patients with metastatic or locally advanced unresectable TCC of the bladder, survival is prolonged with cisplatin-based combination chemotherapy. However, durable complete remissions in patients with advanced disease are rare, and median TTP is short. In an updated report of the randomized trial comparing MVAC with GC, survival at 5 years was 15.3% and 13%, respectively (P = not significant) [5]. These results confirm that TCC is a chemotherapy-sensitive disease, that GC is an appropriate therapy, and that improvements in first-line chemotherapy may yield improved progression-free and overall-term survival for patients with this disease. Recently reported data from the randomized phase 3 study of GC versus GC and paclitaxel did not show a significant advantage for the triple combination [38]. As a result, GC remains standard of care for patients with advanced TCC.

Inhibition of VEGF using an anti-VEGF monoclonal antibody inhibits the growth of several human cancers in nude mice [39]. Bevacizumab, a recombinant humanized murine monoclonal antibody against VEGF, has shown significant clinical activity in other cancer types. Addition of bevacizumab to chemotherapy has been shown in phase 3 studies to improve overall survival in lung (22% improvement) and colorectal cancer (30% improvement with first-line and 19% improvement with second-line therapy) using different chemotherapy regimens, and to improve progression-free survival in breast cancer (49% improvement) [40–43]. In addition, there is a case report from M.D. Anderson Cancer Center of responses to bevacizumab monotherapy in a patient with metastatic chemotherapy-refractory TCC [44]. The evidence supporting the addition of bevacizumab to chemotherapy and the known importance of VEGF in preclinical testing suggest that administering bevacizumab with standard chemotherapy may lead to significant improvements in patients with advanced TCC. This strategy is being tested in a phase 2 study of bevacizumab in combination with GC in patients with advanced or metastatic disease, and will be advanced in a US intergroup phase 3 study comparing the same regimen with chemotherapy alone. This combination is also being tested as neoadjuvant therapy, as is the addition of bevacizumab to neoadjuvant dose-dense MVAC chemotherapy. Bevacizumab also is being tested in combination with gemcitabine and carboplatin in patients ineligible for cisplatin chemotherapy. If the addition of bevacizumab to chemotherapy improves progression-free