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REVIEW

Current and Emerging Strategies for the Management of Bladder Cancer

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Abstract: Treatment strategies and outcome of bladder cancer depend on tumor progression. Non-muscle invasive urothelial cell carcinoma (NMI-UCC) is generally treated by transurethral resection (TUR). In addition, intravesical therapy is often followed to prevent the recurrence; however, its effect is not still enough. On the other hand, the prognosis of bladder cancer patients with muscle-invasive and/or metastatic tumors is poor, despite the availability of various therapies. Although radical cystectomy is the "gold standard" for patients with muscle-invasive disease, high frequency of recurrence and decreased quality of life are major disadvantages associated with this procedure. In recent years, various newly developed treatment strategies have progressed to clinical trials for the perioperative treatment of muscle-invasive cancer and for systematic therapy for advanced bladder cancer. Here, we review the current and emerging therapeutic strategies and discuss the recent clinical trials of anti-vascular endothelial growth factor (VEGF) family- and anti-endothelial growth factor receptor (EGFR)-based therapies.

Keywords: bladder cancer, adjuvant therapy, vascular endothelial growth factor, endothelial growth factor receptor, clinical trials

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Introduction

Bladder cancer is a common malignancy with approximately 350,000 new patients and 15,000 deaths worldwide per year.[1] Bladder cancer predominantly presents as a papillary and non-muscle-invasive (superficial) disease. Such non-muscle invasive of urothelial cell carcinoma (NMI-UCC) is usually treated with transurethral resection (TUR), and shows a relatively good prognosis when it is low grade and when complete TUR is performed. However, approximately 30%~60% of NMI-UCC recur after the primary treatment, and 30% of them progress to the muscle-invasive and/or metastatic disease.[2] Furthermore, up to 50% of these tumors recur despite appropriate surgery and are potentially lethal.[3] The treatment goal in NMI-UCC is therefore the prevention of tumor recurrence and progression, and the most commonly used method is intravesical therapy. Although extensive research has been conducted on the efficacy and side effects of various agents and methods of intravesical therapy, there are still conflicting opinions regarding suitable agents, therapy duration and intervals, patient selection criteria, and the type of maintenance therapy. On the other hand, several new therapeutic strategies have been reported in recent years.

In contrast to NMI-UCC, muscle-invasive cancer is one of the most aggressive epithelial tumors and lethal because the invasive step often leads to subsequent metastasis. Untreated advanced/metastatic bladder cancer results in death within 2 years of diagnosis in over 85% of patients.[4] Radical cystectomy represents the primary therapeutic modality and the "gold standard" for the treatment of patients with clinically localized muscle-invasive bladder cancer. However, despite treatment with radical cystectomy, early systematic dissemination and/or local recurrence often occur, and patients ultimately succumb to advanced bladder cancer. Currently, the 5-year survival rate after radical cystectomy is under 50%, and this rate is worse in high-risk patients (T3 to 4 and/or positive nodes).[5–8] Perioperative therapy can be administered before or after surgery to improve the prognosis and extend the survival period in these patients. Although conventional cytotoxic therapies such as chemotherapy and/or radiation therapy are commonly used in these cases, their therapeutic effect in down-staging tumors or improving survival after surgery are controversial.[9,10] Although various trials have been carried out, satisfactory results have not yet been obtained. The outcome of patients with metastatic disease is also extremely poor, despite the availability of various treatment options. There is a general agreement that new treatment strategies and therapeutic targets for bladder cancer patients with advanced (muscle-invasive and/or metastatic) disease are needed. On the other hand, most of these patients place a high value on the maintenance of their quality of life (QOL) after treatment. Radical cystectomy can result in a substantial loss of QOL despite the progress in surgical techniques. Bladder preservation therapy is therefore important, and the development of new techniques and the improvement of existing ones are essential.

Based on the existing data on the molecular biology and genetics of bladder cancer, various factors have been proposed as therapeutic targets. A significant number of clinical trials have been carried out using molecular targets for intravesical, perioperative, and systemic therapy. Angiogenesis is necessary for the survival and proliferation of bladder cancer cells by promoting the development of new vessels to supply oxygen and nutrition. In addition, newly developed vessels generate a pathway for the movement of cancer cells from the primary tumor to distant organs. The regulation of angiogenesis is therefore considered a promising therapeutic target in many malignancies, and the effects of anti-angiogenic therapy have been reported in various cancer treatments.

The present manuscript describes the current therapeutic strategies and trials of perioperative therapy, prevention therapy, and systematic chemotherapy in patients with bladder cancer. At first, we make reference to current and emerging strategies for the management of NMI-UCC. Next, the current therapeutic strategies and trials of perioperative therapy and systematic chemotherapy in patients with advanced bladder cancer are discussed. In addition, to understand these treatment strategies, the clinical and pathological significance of angiogenesis and mechanisms regulating the development of new vessels in bladder cancer are also discussed.

Treatment for non-muscle invasive bladder tumors

In NMI-UCC, especially carcinoma in situ (CIS), many urologists and medical oncologists agree that bacillus

Calmette-Guérin (BCG) and several anti-cancer agents including mitomycin C (MMC) and epirubicin are the most effective therapeutic tools currently available.[11–13] However, optimum method including regimen and duration are still unknown.[13] In 2010, a randomized trial regarding the recurrence-preventing efficacy of maintenance BCG intravesical therapy for NMI-UCC is reported.[14] In their study, the patients who received complete TUR were randomized into 3 groups; a BCG maintenance group (n = 41; 81 mg, instilled once weekly for 6 weeks, followed by three once-weekly instillations at 3, 6, 12, and 18 months), a BCG non-maintenance group (n = 42; 81 mg, instilled once weekly for 6 weeks), and an epirubicin group (n = 32; 40 mg, instilled nine times). At the 2-year median point, the cumulative recurrence-free survival rates in maintenance BCG, non-maintenance BCG, and epirubicin groups were 84.6%, 65.4%, and 27.7%, respectively. Thus, maintenance therapy with BCG clearly prolonged the recurrence-free survival compared to that with non-maintenance BCG or epirubicin. On the other hand, there is report regarding a randomized trials of thermochemotherapy with mitomycin-C.[15] In this study, 83 patients were randomly assigned to receive either MMC intravesical thermothemotherapy or MMC intravesical therapy alone. At the median follow-up for tumor-free patients (91 months), the 10-year disease-free survival rates were 53% and 15%, respectively. In addition, the high rate (86%) of bladder preservation was also showed in MMC intravesical thermothemotherapy group.

In addition to such device made used of conventional drugs, treatment strategies by new instrument also have been reported. For example, a study of photodynamic therapy (PDT) using chlorine e6-polyvinylpyrrolidone (Ce6-PVP) for bladder sparing treatment in high risk NMI-UCC bladder cancer patients was reported.[16] Interestingly, this therapy was performed in patients with recurrent NMI-UCC after intravesical BCG failure. Unfortunately, although this report is pilot study with a small number of patients (n = 5), PDT has been investigated with anticipation. On the other hand, combination therapy of laser and intravesical instillation of epirubicin was reported to be safety and efficacy for multiple tumor of NMI-UUC.[17] Furthermore, in recent years, new strategies using molecular target therapy have been suggested based on in vivo and in vitro experimentation. The multikinase inhibitor sunitinib can enhance BCG-mediated cytotoxicity in transitional cell carcinoma by the activation of apoptosis.[18] Thus, although further investigation leading to new developments is necessary, the outcome of patients with MNI-UCC is expected to improve.

Angiogenesis in Bladder Cancer

Angiogenesis refers to the formation of new blood vessels and the development of new branching vessels from the existing vasculature. This process is crucial for the growth and progression of tumors because it is essential for the supply of oxygen and nutrients to the tumor cells. In addition, these vessels also constitute the pathway for the dissemination of malignant cells from primary tumors. Tumor growth and metastasis are dependent upon angiogenesis in almost all malignancies.[19] In 1994, the relationship between the degree of angiogenesis and clinical significance in patients with bladder cancer was reported for the first time.[20] Since then, many investigators have reported that microvessel density (MVD), a surrogate marker of angiogenesis, is associated with muscle invasion, metastasis, and survival.[21–23] Actually, angiogenesis is suggested to be one of the most promising therapeutic targets for the regulation of tumor progression and improvement of the prognosis of bladder cancer, especially in advanced stages of the disease.

Vascular endothelial growth factors (VEGFs), which are the most important angiogenic stimulators, play crucial roles in the recruitment and proliferation of endothelial cells. There are more than 7 VEGF family members described to date.[24,25] Among the members of the VEGF family, VEGF-A (VEGF-A is commonly referred to as VEGF) has been the most extensively studied pro-angiogenic factor, and cancer cells and their supporting infiltrating immune cells and mesenchymal cells have been shown to secrete VEGF-A.[26] In bladder cancer, increased expression of VEGF was first reported in 1993.[27] Since then, the clinical and pathological significance of the mRNA and protein expression of VEGF in bladder cancer has been demonstrated, and its roles in cancer progression and prognosis have been well studied. The biological functions of VEGFs are mediated by their interactions with specific receptors including VEGF-receptor (R)-1 (known as fms-like tyrosine

kinase or Flt-1), VEGFR-2 (KDR), and VEGFR-3 (Flt-4). VEGFR-1 and VEGFR-2 are speculated to be associated with only angiogenesis because they are predominantly expressed on the endothelial cells of blood vessels.[28] These receptors are candidates as targets for anti-angiogenic therapy in bladder cancer.

In addition to members of the VEGF family, the endothelial growth factor receptor (EGFR) is also associated with angiogenesis in various pathological conditions. The EGFR family consists of 4 structurally related receptors, for which a variety of different ligand has been characterized. There is a general agreement that EGFR plays important roles for malignant aggressiveness in various malignancies including bladder cancer. That is, most urothelial cancer cell lines show over-expression of EGFR.[29] Increased expression of EGFR was detected in human bladder cancer cells, and this over-expression was associated not only with grade and stage, but also with tumor progression and survival in bladder cancer patients.[30–32] Furthermore, metastases from transitional cell carcinoma of urinary bladder showed over-expression of EGFR.[33] Based on these results, there is a general agreement that EGFR is a potential and useful therapeutic target in bladder cancer. EGFR inhibitors have demonstrated significant anti-tumor effects, in part due to their anti-angiogenic effects.[34–37] In bladder cancer, EGFR has also been associated with tumor invasion and metastasis through the regulation of angiogenesis and cell proliferation in an orthotopic cancer model.[38] The EGFR inhibitor (C225) was found to inhibit angiogenesis in transitional cell carcinoma in a mouse orthotopic model.[35,36] In addition, the selective EGFR tyrosine kinase inhibitor gefitinib ("Iressa") suppressed bladder cancer growth through the regulation of angiogenesis.[39] In a separate study, gefitinib was shown to inhibit tumor growth in a similar model.[37] EGFR has therefore been considered a potential therapeutic target for the treatment of malignancies in preclinical studies. Several FDA-approved EGFR inhibitors are currently available, and their anti-tumor and therapeutic effects in several cancers including lung cancer, colorectal cancer, and head and neck cancer continue to be investigated.[40,41] However, several trials have shown that although these drugs cause tumor regression, survival benefit is not seen.[40,41] Anti-EGFR monotherapy is speculated to have no remarkable effect in the prevention of tumor progression and survival of bladder cancer cells, and so, combination therapies with anti-EGFR and other drugs were investigated. Combination therapy with gefinitib and docetaxel inhibited tumor growth in transitional cell carcinoma in a mouse orthotopic model.[37] In addition, paclitaxel was reported to enhance the anti-tumor effect of C225 in a mouse model.[42] Furthermore, anti-tumor effects of cisplatin were enhanced by treatment with anti-EGFR antibodies in a xenograft model.[43]

Interestingly, VEGF activity is often linked to the EGFR signaling axis in bladder cancer. EGFR-mediated activation of EGF signaling leads to up-regulation of VEGF expression.[44] On the other hand, VEGF secretion in a transitional cancer cell line (253J B-V) was reduced by C225,[35] and a similar phenomenon was detected in an orthotopic xenograft model using immunohistochemistry and in situ hybridization. In addition, gefinitib-mediated blockage exerts an anti-angiogenic effect, in part by modulating VEGF production in bladder cancer cells.[45] Based on these findings, the VEGF family and EGFR are potential targets in patients with bladder cancer.

Treatment for Advanced/Metastatic Bladder Cancer

For the last 2 decades, cisplatin-based combination regimens have been recognized as the standard chemotherapy for patients with advanced bladder cancer. The response rate to methotrexate, vinblastin, doxorubicin, and cisplatin (MVAC) therapy was reported to be superior to that to single-agent cisplatin therapy in patients with metastatic bladder cancer,[46] and it continues to be the most common and useful regimen for these patients.[47] However, in recent years, gemcitabine and cisplatin (GC) therapy has supplanted MVAC as the standard chemotherapy for advanced bladder cancer. GC therapy excels MVAC therapy in terms of tolerability and toxicity. The incidence of febrile neutropenia is 2% and 14% in GC therapy and MVAC therapy, respectively. However, there are no significant differences ($P = 0.75$) in median survival between patients receiving GC therapy (14.7 months) and MVAC therapy (15.2 months).[48] In addition to gemcitabine, various clinical trials with new anti-cancer agents including ifosfamide,[49] oxaliplatin,[50] and paclitaxel[51] have been performed to investigate their impact on the outcome and their safety. However, although some of these single agents

showed significant anti-tumor effects, the results obtained were not satisfactory. These agents have therefore been evaluated as combination partners in other active regimens for first- and/or second-line systematic therapies.[52–55] The anti-tumor effects and impact on long-term survival of these combination chemotherapies cannot be determined accurately at present; however, many urologists and medical oncologist speculate that new treatment strategies are necessary to achieve significant improvements in the outcome. Currently, carboplatin is often substituted for cisplatin in advanced bladder cancer patients with renal dysfunction. The therapeutic effects of carboplatin-based chemotherapy are reported to be inferior to those of cisplatin-based therapies.[56] Similar results were reported in a comparison study of gemcitabine plus cisplatin versus gemcitabine plus carboplatin in advanced urothelial carcinoma.[57] Although further studies are necessary for an accurate assessment of the efficacy of carboplatin-based chemotherapy in patients with bladder cancer, these results provide important information on treatment options.

VEGF Family- or EGFR-Based Targeted Systematic Therapy for Advanced/Metastatic Bladder Cancer

In recent years, various preclinical and clinical trials using VEGF-targeted therapy have been performed in patients with high-risk bladder cancer. The most widely investigated agent used for targeting VEGFs is bevacizumab, and it is the first anti-angiogenic drug to gain FDA approval. It is a recombinant humanized monoclonal antibody that binds to and neutralizes VEGF-A.[58] This drug was already approved by the FDA for the treatment of colorectal cancer, lung cancer, and renal cell carcinoma, and there is general agreement on its effectiveness.[59–61] However, most of these trials were based on the anti-tumor effects of combination therapy of bevacizumab and other anti-cancer agents. The effect of bevacizumab as monotherapy was studied in a variety of solid cancers; however, this agent failed to show a significant clinical effect or anti-tumor activity.[62] In addition, there are no reports showing the effectiveness of bevacizumab monotherapy for the treatment of bladder cancer. On the other hand, several combination therapies including bevacizumab have been designed for bladder cancer patients. For example, a randomized phase III trial of GC versus GC + bevacizumab is being carried out in metastatic bladder cancer patients (NCT00234494) by the Cancer and Leukemia Group B (Table 1).

In contrast to the number of studies on VEGF-A-neutralizing antibodies, there are few clinical studies on the anti-tumor effects of targeting VEGFR-1 or the binding of VEGF-A to VEGFR-1. The effect of an anti-VEGFR-1 peptide on the inhibition of tumor growth and metastasis of colon cancer cells was reported in animal experiments.[63] Another method for the inhibition of VEGFR activity using catalytic RNA molecules known as ribozymes has been reported. Ribozymes can down-regulate VEGFR function by specifically cleaving the VEGFR m-RNA. RPI.4610 (angiozyme) is a stabilized ribozyme that specifically targets the pre-RNA of VEGFR-1 and its soluble form, sVEGFR-1. In a phase I study, angiozyme showed anti-tumor effects in various malignancies.[64] Although the efficacy and toxicity of angiozyme have been studied in gynecological diseases,[65,66] the effect of this agent has not been investigated systematically in patients with bladder cancer. Combination therapies with RPI.4610, carboplatin, and paclitaxel have been assessed in advanced solid tumors including 1 bladder cancer patient, who interestingly showed a complete response without severe side effects.[67] Further studies on the efficacy and safety of RPI.4610-based regimens are planned for patients with bladder cancer.

Various preclinical and clinical trials on the anti-angiogenic and anti-tumor effects of VEGFR-2 have been conducted. The most extensively studied VGEFR-2 inhibitors are sunitinib and sorafenib, which are classified as multi-tyrosine kinase inhibitors. In addition to VEGFR-2, other target molecules of sunitinib are VEGFR-1, PDGFR, c-Kit, Flt-3, and RET.[68] Similarly, sorafenib also targets VEGFR-3, Raf, and PDGFR.[69] In the field of urological oncology, these agents are recognized as some of the most effective anti-tumor drugs for advanced RCC.[70,71] However, the use of these inhibitors as single agents for the treatment of advanced bladder cancer was shown to have minimal effects in several trials.[72] FDA approval of these drugs in urological cancer has been limited to RCC, but not to bladder cancer. However, the design of combination therapies of sorafenib or sunitinib with cytotoxic chemotherapy or other molecular-targeted

Table 1. Clinical trials of angiogeneis-related factor-based therapy.

Drug (+combined drugs)	Target	Phase	Objective	IDs of trials
Bevacizmab	VEGF			
(CDDP + GEM)		III	Advanced	NCT0094233
(CBDCA + GEM)		II	Advanced	NCT00588666
(CDDP + GEM)		II	Neo-adjuvant	NCT00268450
(PAC)		II	Adjuvant	NCT00268450
Sunitinib	Multiple-TK			
(Nothing)		II	Advanced	NCT00393796
(Nothing)		II	Advanced	NCT00526656
(Nothing)		II	Advanced	NCT01118039
(Nothing)		II	Advanced	NCT00578526
(CDDP + GEM)		II	Advanced	NCT00821327
(CDDP + GEM)		II	Advanced	NCT01089088
(CDDP + GEM)		II	Neo-adjuvant	NCT00847015
(Nothing)		II	Neo-adjuvant	NCT00859339
(Nothing)		II	Adjuvant	NCT01042795
Sorafenib	Multiple-TK			
(CDDP + GEM)		II	Advanced	NCT00461851
(Radiation)		I	Advanced	NCT00544609
Pazopanib	PDGFR, VEGFR			
(Nothing)		II	Advanced	NCT00471536
(Nothing)		II	Advanced	NCT01031875
Gefitinib	EGFR			
(CDDP + GEM)		II	Advanced	CALBG-90102
Cetuximab	EGFR			
(CDDP + GEM)		II	Advanced	NCT00645593
Vandetanib	VEGFR, EGFR			
(CBDCA + GEM)			Advanced	WCTU-TOUCAN
Brivanib	FGF, VEGF	II		
(Nothing)			Advanced	NCT00633789
Erlotinib	EGFR			
(Nothing)		II	Neo-adjuvant	NCT00380029
(Nothing)		II	Neo-adjuvant	NCT00749892

drugs is underway.[73] VEGFR-2 was also reported to be expressed in urothelial cancer cell lines.[74] In addition, VEGFR-2 expression was detected in bladder tumors, and its expression level correlated to the pathologic stage.[75] Based on these facts, the anti-tumor effect of a monoclonal antibody targeted against VEGFR-2 (DC101) was investigated in an orthotopic bladder cancer xenograft model.[76] This study demonstrated that combination therapy with DC101 and paclitaxel reduced the incidence of lymph node metastasis in a murine model of metastatic transitional cell carcinoma of the bladder compared to that in a control group and in a group treated with each agent alone.[76] Interestingly, this combination therapy affected mainly smaller immature vessels and not the larger established vessels. This finding indicates that DC101 may inhibit only angiogenic blood vessels formed by carcinogenesis. However, other investigators reported that tumor angiogenesis in bladder cancer was not inhibited completely by DC101 alone in human bladder cancer xenografts.[77] Investigators generally agree that anti-VEGFR-2 targeted monotherapy is inefficient for the inhibition of tumor growth and to prolong survival in patients with bladder cancer. Table shows the results of clinical trials using VEGF family-related molecules for patients with advanced/metastatic bladder cancer.

EGFR has also been identified as an interesting and exciting target in bladder cancer. As shown in

Table, various EGFR-targeting agents are being evaluated or are in the process of undergoing clinical trials. Among them, a phase II trial of CDDP, gemcitabine, and gefitinib did not yield sufficiently promising results for the further evaluation of these drugs in a phase III setting.[78] On the other hand, various new EGFR inhibitors such as zactima (ZD 6474, a small molecule receptor tyrosine kinase inhibitor of EGFR and VEGFR-2 and VEGFR-3) are being assessed as the frontline therapy for advanced/metastatic bladder cancer. Interestingly, zactima is used in combination with docetaxel for the treatment of metastatic cancer. In recent years, EGFR and VEGFR inhibition has been found to increase chemotherapy sensitivity in bladder cancer cells.[79] Based on these findings; this regimen is expected to result in clinical benefit and improvement of outcome. Further clinical trials and studies are necessary to assess the benefit of EGFR-targeted therapy.

Perioperative Therapy in Patients with Muscle-Invasive Cancer

The standard procedure for muscle-invasive bladder cancer is immediate radical cystectomy with pelvic lymphadenectomy. However, as mentioned above, the local control rates are not satisfying with such surgery alone, especially for tumors with peri-vesical invasion. In addition, distant metastasis occurs in up to 50% of these patients, and most of them die due to disseminated cancer cells. Based on these facts, perioperative (neoadjuvant and/or adjuvant therapy) therapy is performed in a selected group of bladder cancer patients.

Neoadjuvant therapy is intended for patients with operable muscle-invasive disease. This treatment strategy is designed to treat micro-metastases present before radical surgery. Most investigators agree that single-agent therapy with conventional anti-cancer agents including cisplatin is insufficient to obtain a clinical benefit.[80,81] Therefore, as neoadjuvant therapy, CDDP-based combination chemotherapy is commonly used. However, there was no clear evidence that this therapy would increase disease-free and/or cause-specific survival. By the European Organization for Research and Treatment of Cancer (EORTC) and the Medical Research Concil (MRC), the largest randomized trial of neoadjuvant cisplatin-based chemotherapy was performed.[82] In this trial, 976 patients with muscle invasive bladder cancer were randomly assigned 3 cycles of CMV (cisplatin, methotrexate, and vinblastine, n = 491) or no chemotherapy (n = 485). At the median follow-up of patients still alive at 4.0 years, median survival in the CMV group was 44 months compared with 37.5 months for the no chemotherapy group. In addition, 32.5% of cystectomy samples contained no tumor after neoadjuvant chemotherapy. However, they concluded that neoadjuvant chemotherapy did not give the 10% improvement in 3-year survival (55.5% versus 50.0%, $P = 0.075$). On the other hand, several studies showed that cisplatin-based neoadjuvant therapy combined with cystectomy is associated with an improvement in the prognosis of patients compared to cystectomy alone.[83–86] Urologists and medical oncologists are sometimes reluctant to use this therapy due to concerns regarding toxicity and tumor progression during neoadjuvant therapy administration. In particular, cisplatin-based regimens are often difficult and must be administered with caution in patients with renal function disorder and advanced age. With regard to the delay of radical surgery, several reports have shown that a long interval (over 12 weeks) between the diagnosis of muscle invasion and performance of radical cystectomy is associated with undesirable outcomes in bladder cancer patients.[87,88] In addition, although some investigators fear that neoadjuvant therapy may increase the incidence of perioperative morbidity, there are no reports that conclusively support this negative effect.[89,90] Many urologists and investigators are not fully aware of the benefits of this strategy because a large randomized trial and meta-analysis showed that the addition of chemotherapy to local therapy including radical cystectomy resulted in a benefit of approximately 5%.[9,89] In recent years, newer active chemotherapeutic agents such as gemcitabine and taxanes have been used in the neoadjuvant setting. However, these protocols remain experimental because of the lack of large and good-quality randomized trials.

Similar to its use in neoadjuvant therapy, CDDP-based chemotherapy is the standard adjuvant therapy regimen after radical cystectomy. There are, however, few adequate randomized clinical trials that analyze the anti-tumor effects and prognostic efficacy of this

therapeutic strategy.[91] Several reports have shown that adjuvant CDDP-based chemotherapy increased the overall and disease-specific survival.[92,93] Therefore, bladder cancer patients with high T stage (>T3) or positive nodes should be considered for adjuvant therapy.[92] On the other hand, several studies failed to show clinical or prognostic benefits of this therapy.[94,95] Carboplatin- or taxol-based therapies are also applied in patients with renal dysfunction, poor performance status and/or postoperative complications; however these therapies are relatively rarely used in such patients because they usually cannot receive additional therapy.[92] Furthermore, similar to chemotherapy in patients with advanced cancer, carboplatin-based regimens showed no benefit as perioperative treatment in phase II trials.[96,97] Thus, although a large randomized control study is necessary to define the benefits and risks of adjuvant chemotherapy, carboplatin based-chemotherapy is not currently recommended. The design of new strategies based on basic and preclinical studies is also important and essential. Both neoadjuvant and adjuvant therapies have advantages and disadvantages. The main difference between these 2 therapies is whether the bladder is preserved or not. To date, a comparison of the therapeutic efficacy of neoadjuvant and adjuvant therapy has not been carried out through good-quality randomized trials. A small comparative study on 140 patients demonstrated that there were no significant differences between these 2 strategies.[98] However, a strict comparison is difficult because clinical stage does not always reflect pathological progression.

There are several clinical trials using anti-angiogenic agents including VEGF family- and EGFR-related molecules. Bevacizumab, cisplatin, and gemcitabine were used for patients with locally advanced but resectable bladder cancer.[99] In addition, the results of a phase II trial of neoadjuvant erlotinib, an orally available small molecule tyrosine kinase EGFR inhibitor (Tarceva; 150 mg/day × 4 weeks), on 20 patients with clinical stage T2 disease showed that 5 patients (25%) were pT0, and 7 (35%), pT1 stage on examination of their specimens of radical cystectomy.[100] The most common side effect noted was skin rash (15 of 20 patients, 75%); in addition, significant adverse events were limited to only skin rash in 4 patients (20%), and to fatigue and vagal reaction in 1 patient each. Although additional studies are essential to determine the clinical efficacy and toxicity of this therapeutic strategy, this regimen is favored for neoadjuvant therapy because of the relatively mild side effects and single-agent clinical activity. Table shows a summary of anti-angiogenesis-based perioperative adjuvant therapies in patients with muscle-invasive bladder cancer.

Strategies for Bladder Preservation

Although radical cystectomy can be performed safely with an acceptable morbidity and a 4.9% incidence rate of major complications,[101] the decline in QOL is inevitable. To preserve bladder function and maintain QOL, various strategies are used for the treatment of muscle-invasive cancer. In most bladder preservation programs, the success of complete TUR is essential and a minimum requirement. Various additional treatments such as chemotherapy, radiation therapy, or combination therapy are then used to eliminate residual cancer cells in the muscle layer.[102–104] Unfortunately, there is little information on the efficacy of anti-angiogenic agents in preservation therapy. In addition, the inclusion criteria for preservation therapy programs need to be defined. Several reports have demonstrated that small tumor size (<5 cm), complete TUR, low clinical stage, and absence of hydronephrosis are the most important factors for survival.[102,103,105,106] In particular, the completeness of TUR has been reported to be the strongest prognostic factor for overall survival by multivariate analysis.[106] However, the effects of this treatment strategy must be equivalent to those of other treatment options including radical cystectomy to justify its application, and data acquisition to help determine the best treatment strategy is essential.

In this section, the results of 2 interesting reports are described. First, balloon-occluded arterial infusion (BOAI) of an anti-cancer agent and concurrent hemodialysis (HD) as preservation therapy seems unique and interesting. In this program, patients clinically diagnosed with muscle-invasive diseases underwent complete TUR to establish the histological diagnosis. Next, patients suspected of pT2–4 muscle-invasive bladder cancer without distant metastasis received chemotherapy by BOAI of CDDP and concurrent HD, followed by radiation therapy. This method resulted in complete response

in 39/43 patients (90.7%). Interestingly, none of the patients developed recurrent disease or metastasis within 36–683 weeks (mean = 162 weeks), and none suffered from any severe toxicity of grade 3 or above.[107] The second treatment is a combination of chemotherapy, radiation therapy, and hyperthermia. Deep regional hyperthermia is reported to improve the complete response and survival rates when combined with radiation and/or chemotherapy.[108,109] A recent study utilizing a combination therapy of radiation, 5-fluorouracil/CDDP, and regional hyperthermia reported a pathological complete remission and 3-year overall survival of 95% and 82%, respectively, in addition to bladder preservation.[109] The development of these methods is expected to provide new and useful options with high efficacy and relatively low toxicities.

Conclusion

In NMI-UCC, intravesical therapy using BCG or anti-cancer agents including MMC are commonly performed. In recent years, various modified intravesical therapy including maintenance BCG therapy, thermochemotherapy, and new instrument have been reported. In advanced bladder cancers, CDDP-based chemotherapy is used most commonly among the current treatment strategies. In addition, new chemotherapeutic agents such as gemcitabine and taxanes are being developed as useful tools. In fact, GC therapy is recognized as standard regimen in many bladder cancer patients with advanced disease. By the development of molecular-targeted therapy, various clinical trials of monotherapy and combination therapy with anti-angiogenic drugs for bladder cancer are now in progress. In this manuscript, we paid attention to anti-angiogenesis therapy using inhibitor of VEGF-family or EGFR. In near future, new these strategies may change the prognosis and outcome in patients with bladder cancer.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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