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Chapter 4

Current Status and Clinical Trials of Paclitaxel-Containing Therapy for Urothelial Cancer

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Abstract

Urothelial cancer (UC) arising from the urinary bladder, renal pelvis, or ureter is a common cancer in adult males. In general, UC is recognized as chemo-sensitive and patients with advanced-stage lesions including metastatic UC are treated using chemotherapy-based methods. At present, combination therapy with gemcitabine and cisplatin (CDDP) is standard in patients with such advanced UC. MVAC therapy comprising methotrexate, vinblastine, doxorubicin, and CDDP is also used for these patients. However, unfortunately, most of these patients experience relapse and no standard salvage therapies have been devised for use after CDDP-containing regimens. In recent years, various new chemotherapeutic agents and regimens have been reported as effective

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and safe for CDDP-resistant UC, and various targeted and anti-angiogenic therapies are also performed. However, most of these approaches have been described in preliminary studies and further investigations are necessary to confirm their clinical feasibility. Clinical studies are thus in progress all over the world. Paclitaxel (PTX) appears effective against UC. Previous reports have identified PTX monotherapy as an active first line chemotherapeutic regimen. In addition, this agent is considered a good option for salvage therapy, because it is well tolerated and safe. On the other hand, whether PTX monotherapy or PTX-based combination chemotherapy offers satisfactory anti-tumoral effects and prolonged survival in patients with CDDP-resistant UC remains unclear. The aim of this study was to clarify the current status of PTX-containing chemotherapy as second line therapy for patients with UC. In addition, we introduce clinical trials of PTX-containing chemotherapies and combination therapies with PTX and molecular-targeted therapy for advanced UC. We also describe delivery systems and intravesical therapies using PTX. This chapter therefore introduces comprehensive and wide-ranging information regarding the current status of PTX-based therapies in patients with UC.

Introduction

Urothelial cancer (UC) of the urinary bladder is the fourth-most common cancer in men and approximately a quarter of patients show advanced disease at diagnosis [1]. While UC of the upper urinary tract is relatively rare, it has a high frequency of metastasis due to the upper urinary tract's anatomical characteristics like a thin muscle layer, proximity to the kidneys, and rich lymphatic drainage. In addition, UC is recognized to have high malignant potential, and the median survival of patients with metastatic disease who receive no aggressive treatment is 4-6 months. Discussion of treatment strategies for patients with advanced UC is thus essential.

In almost all cancers, chemotherapy represents a common and important approach to treatment, particularly in advanced-stage and metastatic disease. In general, UC arising from the upper urinary tract or urinary bladder is recognized as chemo-sensitive [2]. Among various chemotherapeutic agents, cisplatin (CDDP) is considered the most useful and effective against UC, as with various other malignancies. In the 1990s, the "gold standard" chemotherapy for the treatment of patients with advanced UC was the MVAC regimen comprising methotrexate, vinblastine, doxorubicin, and CDDP, among various CDDP-containing regimens [3,4]. This regimen is effective

compared to cisplatin monotherapy in patients with metastatic UC, but is relatively toxic and shows a high frequency of severe adverse events [5] . That is, response rates for MVAC as a first line therapy for treating advanced UC are reportedly approximately 70%, but the incidence of drug-related high-grade toxicity including death is approximately 60% [3-5]. Preventing and reducing adverse events is thus problematic with the MVAC regimen.

In 2000, the combination of gemcitabine (GEM) and CDDP was reported in a randomized phase III study to show similar anti-tumoral efficacy to the MVAC regimen, but with lower toxicity [6]. Actual frequencies of neutropenic fever with this CG regimen and the MVAC regimen were 2% and 14%, respectively. In addition, the mortality rate due to toxicity was 1% on the GC regimen and 3% on the MVAC regimen. The GC regimen is thus currently considered the gold standard in patients with advanced UC. These CDDP-based combination chemotherapies are associated with clinical remission in about half of advanced UC patients [7] , and such regimens are commonly used as first line chemotherapy.

Unfortunately, most patients responding to CDDP-based chemotherapies develop disease progression, with the cancer often becoming highly aggressive. In fact, almost all patients experience disease recurrence within the first year, and median survival is approximately 1 year [6,8]. As a result, many urologists, medical oncologists, and researchers pay special attention to second line chemotherapies, but approved and established therapeutic options remain lacking.

In addition to such failings, CDDP-based regimens are unavailable for treatment of some patients because of their nephrotoxicity and other comorbidities. Carboplatin is a platinum-based organic drug that has been used as a substitute for CDDP in various combinations because of its lower nephrotoxicity [2,9]. However, the anti-tumoral effects of carboplatin are generally recognized as inferior to those of CDDP in UC patients. Similar results have also been reported between CDDP- and carboplatin-based chemotherapies for the treatment of advanced UC [10]. That is, overall response and complete response rates with CDDP-based regimens were 36-71% and 13-25%, respectively, whereas rates with carboplatin-based regimens were 28-56% and 0-11%, respectively. Aside from these relative merits between regimens, the anti-tumoral efficacy of carboplatin-based regimens remains unsatisfactory.

Development and clinical trials of non-cisplatin-based chemotherapeutic agents and non-CDDP-based regimens are thus important to improve the outcomes of patients with advanced UC. In particular, new treatment strategies

and regimens are becoming increasingly important for improving quality of life (QOL) and prolonging survival in patients with CDDP-resistant UC. This chapter pays special attention to paclitaxel (PTX)-based regimens for UC patients, especially in terms of drug delivery system, combination with molecular-targeted agents and intravesical PTX therapy. In addition, our data on changes in QOL score using PTX-based therapy are also introduced. On the other hand, we highlight the lack of basic information on the therapeutic efficacy and safety of conventional PTX-based regimens needed to make routine decisions regarding treatment.

Why PTX?

Several anti-tumoral agents have been reported as useful and safe for the treatment of UC patients. However, unfortunately, such monotherapies have been barely satisfactory in terms of response rate and patient outcomes, particularly for advanced UC. For example, response rates to CDDP monotherapy and carboplatin monotherapy in advanced UC patients are 12-17% and 12-14%, respectively [11,12]. GEM has been extensively studied using various schedules and different settings, and response rates for GEM monotherapy in patients with advanced UC have been reported as approximately 27-29% [13]. On the other hand, PTX monotherapy showed a relatively high response rate (42%) without severe adverse events for patients with advanced UC [14]. PTX thus has the strongest anti-tumoral effect among investigated anti-cancer agents.

PTX exhibits cytotoxic activities via cell cycle arrest and the regulation of apoptotic pathways [15,16], exerting similar anti-tumoral functions to other types of chemotherapeutic agent. On the other hand, PTX can also function as a microtubule inhibitor that acts by promoting tubulin polymerization and stabilization of microtubules [17], representing a unique characteristic. Microtubules play essential roles in cell proliferation and mitosis in cancer cells [18,19]. As a result, anti-microtubule functions lead to G2-M arrest and mitotic cell death [18]. These unique mechanisms represent desirable characteristics for combination with other types of anti-tumoral agent.

PTX-Based Regimens

As mentioned above, PTX monotherapy offers a relatively high response rate as first line chemotherapy, but the response rate for previously treated advanced UC was just 7% [20]. Actually, to the best of our knowledge, clinical studies and case reports have not defined PTX monotherapy as useful or effective as a second line chemotherapy for UC patients. There is thus general agreement that PTX should be used in combination chemotherapy for advanced and/or pre-treated UC.

Representative PTX-based combination therapies include PTX with CDDP and PTX with carboplatin. However, typical response rates are reportedly 35-65% (median survival, 10-12 months), similar to MVAC and the GC regimen [14, 21]. Another representative PTX-based therapy is the GP regimen, combining PTX with GEM. This GP regimen has interesting pharmacokinetic characteristics, in that PTX increases the accumulation of GEM triphosphate as the active metabolite of GEM [22]. In fact, several studies on the GP regimen as a second line chemotherapy have reported favorable results [23,24]. The M-TEC regimen, comprising methotrexate, PTX, epirubicin, and carboplatin, is similar to the MVAC regimen. This regimen has been applied as first line treatment for urinary bladder metastases [25]. In recent years, the anti-tumor effects and toxicity of this regimen as second line treatment after GC therapy were reported by Halim et al.[26]. This prospective phase II study was performed using methotrexate (40 mg/m^2 on day 15), PTX (175 mg/m^2 on day 1), epirubicin (40 mg/m^2 on day 15), and carboplatin (area under the curve, 5) in 40 patients. The overall response rate was 39% and median progression-free and overall survival rates were 12% and 35%, respectively. Finally, the authors concluded that this regimen offers a modest response rate with acceptable toxicity.

In addition to PTX-based combination therapies, sequential therapy with GEM and carboplatin followed by PTX has been reported as a safer first line treatment for 27 patients with advanced UC [27]. This regimen showed a response rate of 40.7% and 3 patients displayed grade 3 neutropenia and anemia as main toxicities. They concluded that this sequential approach seems safe and useful, but failed to improve outcomes due to the small number of patients. Such sequential therapy is expected to improve the anti-tumoral effects and prolong survival for previously treated patients with advanced UC.

Nano-Particle and Drug Delivery System for PTX

PTX is a hydrophobic molecule with poor solubility in water. The micelle-forming vehicle Cremophor EL, a polyethoxylated castor oil, has therefore been used as a solvent. In current commercial formulation, PTX is dissolved in a 1:1 (v/v) mixture of Cremophor EL and dehydrated alcohol. However, this mixture is toxic and can induce side effects such as hypersensitivity reactions and neurotoxicity [28]. In fact, about a third of patients displayed minor hypersensitivity reactions despite routine pre-medication [29]. This infusion therefore needs a prolonged administration time of 3 h and premedication with corticosteroids and antihistamines. In addition, PTX must be prepared in a non-polyvinyl chloride infusion set with an in-line filter to prevent leaching of di-(2-ethylhexyl) phthalate (DHPE) from Cremophor EL, which is a potential hepatotoxin and mutagen [30,31]. To address such problems and unfavorable issues, various studies and trials have been undertaken. In this section, we show two representative strategies, namely nab-PTX and a drug delivery system.

Overview of Nab-PTX

Nab-PTX is a novel albumin-bound nanoparticulate form of PTX. With this modification, nab-PTX has characteristics of increased solubility and drug delivery to cancer cells via biological interactions with albumin receptors to facilitate drug transport across epithelial cells [32,33]. Several studies have shown that nab-PTX offers highly potent inhibition of cell proliferation in various cancers, both in vitro and in vivo [34]. This formulation was approved by the Food and Drug Administration (FDA) in 2005 as a systematic therapy for treating breast cancers that fail to respond to combination chemotherapy for metastatic disease or show relapse within 6 months of adjuvant chemotherapy. In addition, nab-PTX has advantages in terms of a reduced risk of hypersensitivity and eradication of the need for special intravenous tubing. Finally, nab-PTX does not require premedication or prolonged infusion times.

Arterial infusion of chemotherapy has been used for the treatment of local advanced bladder cancer. Interestingly, one phase I study found that hepatic arterial infusion of nab-PTX is safe at doses up to 260 mg/m^2 [35]. In addition, hepatic arterial infusion of nab-PTX in combination with intravenous GEM

and bevacizumab was well tolerated and had anti-tumoral effects for patients with liver metastases [36]. As mentioned above, nab-PTX showed a reduced risk of various adverse events, including hypersensitivity reactions. Various methods of administration are thus possible.

Delivery System

Intra-tumoral delivery of agents is a consistent strategy to provide drug localization within the tumor and minimize exposure of non-target organs. As drug carriers, various types of natural and synthetic polymers have been proposed. However, among these, few have progressed to in vivo or clinical trials, including polymer-based carriers such as in situ gel-forming polymers, thermosensitive polymers, and poly (organophosphazene) hydrogels. What has been investigated is thermosensitive poly (organophosphazene) gel chemically conjugated with PTX [37]. In addition, a PTX-poly (organophosphazene) hydrogel mixture that can be simply prepared by physically mixing PTX with polymer solution showed that this system can accommodate a large dose of the drug in human tumor xenografts [38].

Other investigators have reported that nanoparticle-mediated co-delivery of PTX and a toll-like receptor 4 agonist may suppress tumor growth and enhance immune response in the tumor microenvironment in a mouse model [39]. The authors suggested that treatment with this nanoparticle reverted the immunosuppressive tumor microenvironment to a functionally active state that acts synergistically with chemotherapy for better anticancer response.

In addition, pH-responsive nanoparticles for delivery of PTX have been developed and are reported to improve cytotoxic activity compared to pH-insensitive nanoparticles [40]. In addition, the same study found that these particles can reverse the multidrug resistance of PTX-resistant cancer cells.

The most important determinant of therapeutic effect for PTX is transportation to the cancer cell. In the near feature, advanced technologies are likely to change the therapeutic strategies for the use of PTX in patients with UC.

Targeted Anti-Tumor Agents

Angiogenesis is a key step that primarily involves the generation of new blood vessels from the pre-existing vasculature. This step is essential for tumor growth and cancer cell dissemination from the primary tumor in almost all solid cancers. Proliferation, migration, and tube formation are the most important events of the angiogenic cascade. Partial or full inhibition of these events is thus crucial for anti-tumor activities in various malignancies, including UC. At present, many types of molecular-targeted therapy show anti-angiogenic activity.

PTX leads to cell death via the stabilization of microtubules active in malignant cells. In addition to such cytotoxic activity, PTX is an anti-angiogenic agent that inhibits endothelial cell proliferation, migration, and tube formation [17,41]. However, the main anti-tumoral effects of PTX seem to be achieved through the stabilization of microtubules. As a result, several targeted anti-angiogenic agents have been combined with PTX in trials for various malignancies [42,43].

Another interesting pharmacological characteristic of PTX is that the agent leads to increased levels of sunitinib. Heath et al. [42] reported maximum and total plasma exposures to sunitinib and its active metabolite were increased when given with PTX plus carboplatin in a phase I study of solid tumors. Unfortunately, this phenomenon led to increased risk of adverse events, but is interesting in terms of discussing new treatment strategies using PTX.

In recent years, the anti-angiogenic effects of dual drug-loaded polymeric micelles of PTX and rapamycin have been reported [44]. Rapamycin is an m-TOR inhibitor and causes cell arrest in the G1 phase and suppression of pro-angiogenic factors through down-regulation of hypoxia-mediated pathways [45,46]. Previous reports have shown that the anti-angiogenic activities of rapamycin differ from those of PTX [17,41]. This method takes advantage of each of the anti-tumoral and anti-angiogenic effects from combination therapy and the drug delivery system. In fact, the dual-loaded polymeric micelles exert synergistic anti-angiogenic activity and have strong potential for further development as an anti-angiogenic chemotherapy [44].

Table summarizes clinical trials using molecular-targeted therapy including PTX. The present state and near future of molecular-targeted therapy for UC have been reviewed by many investigators [47-49]. However, we and the authors of these reviews expect improvements in therapeutic efficacy and patient outcomes with the continued development of molecular-targeted

therapies. Even so, innovations and the introduction of radical changes in treatment strategies and anti-cancer agents are necessary to fulfill these dreams.

Table. On-going clinical trials including paclitaxel for urothelial cancers

Combined drug/therapy	Objective	Phase	Start	Status	IDs of trials
Trastuzumab/ Radiation	MIBC after TUR	I/II	2005	Recruiting	NCT00238420
GEM and DOC /	Metastatic/ Unresectable	II	2007	Active	NCT00478361
Lapatinib/	Advanced	I	2006	Recruiting	NCT00313599
Pazopanib/	Refractory	II	2010	Recruiting	NCT01108055
Everolimus/	Advanced/ First	II	2010	Recruiting	NCT01215136
Abraxane/ Intravesical	Refractory	I/II	2007	Recruiting	NCT00583349
Abraxane Carbo GEM/	Neoadjuvant	II	2007	Active	NCT00585689
Abraxane Carbo GEM/	First -Advanced	II	2009	Active	NCT00995488
single/	Second-Advanced	II	2008	Recruiting	NCT00683059

Intravesical Treatment

As mentioned above, the main use of PTX has been for treating advanced bladder cancer, including muscle-invasive bladder cancer (MIBC) and/or metastatic diseases. On the other hand, approximately 60-70% of bladder cancer patients show non-MIBC (NMIBC) at diagnosis, and transurethral resection (TUR) is commonly performed as primary treatment [50]. In almost all NMIBC patients, radical resection is expected as appropriate TUR at that time. Unfortunately, even for bladder tumors with cancer cells limited to the mucosa, recurrences appear in about 70% of tumors and 30% progress to invasive tumors; the high malignant potential is linked to a high risk of subsequent metastasis and poor survival [51,52]. Prevention of recurrence into bladder mucosa is thus important for improving outcome and survival in patients with NMIBC. Intravesical therapy is a common method and several

chemotherapeutic agents or some types of Bacillus Calmette-Guerin (BCG) are considered the best recourse, predominantly depending on stage of disease and presence of carcinoma in situ [53-55]. However, approximately a quarter to half of patients experience recurrence within 5 years after standard TUR and intravesical BCG therapy [53-55]. When such first line intravesical therapy fails, radical cystectomy is the option most likely to improve survival, because effective second line therapies have yet to be established. On the other hand, some patients refuse this life-altering method or are ineligible for the operation due to medical comorbidities or age. Development of novel anti-tumoral agents for intravesical therapy is thus necessary.

Several new anti-tumor agents for intravesical therapy have been studied by urologists and investigators. Comprehensive reviews and interesting investigations regarding strategies to enhance efficacy and current trends in intravesical therapy for NMIBC have been reported [56,57]. The present report thus takes note of intravesical therapy using taxanes.

In 1994, the in vitro activity and urine stability of taxanes, including PTX and docetaxel, were investigated and reported as effective against UC cell lines and stable in human urine for over 4 h [58]. These findings suggest that both PTX and docetaxel may be clinically useful agents for intravesical use against UC. The first human trial of intravesical taxane therapy was reported in 2006, showing an initial response rate for docetaxel of 56% [59]. In addition to this phase I trial, the efficacy and safety of docetaxel have been studied for the management of NMIBC refractory to standard intravesical therapies including BCG [60]. On the other hand, several reports have described 2 h intravesical administration of PTX as sufficient to produce anti-proliferative and apoptotic effects in 70-90% of human bladder tumors, and this agent represents a viable candidate drug for intravesical therapy according to a pharmacokinetic study [61,62]. Similar to docetaxel, PTX seems suitable and useful for intravesical therapy in NMIBC patients. However, to the best of our knowledge, no clinical trials of intravesical therapy have used pure PTX alone. Wosnitzer, et al. [63] used docetaxel and nano-particulate albumin-bound PTX, but not PTX, in a study on predictive markers for intravesical therapy in NMIBC. One major reason that PTX was not used for intravesical therapy was that Cremophor was used to solubilize the drug and, by trapping PTX in micelles, reduced the free fraction of PTX and consequently lowered drug penetration into bladder tissues [64]. On the other hand, the efficacy and safety of intravesical therapy using various PTX-loaded nanoparticles and PTX-based agents have been investigated in animal experiments and clinical studies

[63,65,66]. Those studies showed that effective administration of PTX to cancer cells leads to improvement of the anti-cancer effects against UC cells.

In recent years, a phase I trial of intravesical nanoparticle albumin-bound PTX (ABI-007) was performed for patients with BCG-refractory NMIBC [67]. In that trial, 18 patients received 6 weekly instillations of ABI-007 and no grade 2, 3, or 4 drug-related local toxicities were encountered. A phase II trial is thus being designed to evaluate the anti-tumoral effects of this regimen. In addition, the efficacy and safety of intravesical induction of PTX-hyaluronic acid or PTX gelatin nanoparticles have been investigated in clinical studies for NMIBC patients, including those with BCG-refractory cancer [68,69]. Thus, by improving delivery systems, PTX and its "family" may change treatment strategies, including for the prevention of tumor recurrence in patients with NMIBC.

Conclusion

Paclitaxel-based therapies are useful and promising for patients with UC. In special, development of delivery system, technology of nanoparticle and molecular targeted agents are speculated to benefit for prevention and therapy strategies in patients with UC. Although further studies and clinical trials are necessary for conclusion of these hypotheses, we emphasize that PTX and various drugs derived from PTX are one of key therapeutic agents in present and near future.

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