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Pain Management for Urological Cancer Patients in Palliative Care

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Abstract

Pain mitigation and therapy is one of the most important medical tasks of the urologist, where patients benefit a lot from the basic concepts of analgesia. However, pain resulting from cancer can be more complex than the one after the surgery. Patients that are not receiving regional analgesia should be administered with intravenous or oral non-opioid analgesics in combination with titration. Slow-release of oral opioids is increasingly being used as part of systemic pain management despite little evidence of their efficacy. Continuous epidural infusion is recommended for pain resulting from extensive retroperitoneal and transperitoneal cancers because of its ability to enhance recovery. Additional pain relief-related approaches such as radiation, psychosocial and spiritual needs of the patients have to be considered.

Therefore, a multidisciplinary team of experts is needed to administer etiology-specific pain management and therapeutics. Patients often benefit from multimodal, interdisciplinary pain management techniques comprising psychological and educational approaches, including physiotherapy. This article reviews the pain management techniques for the patients under palliative care. In addition, it presents the cases of urological cancer patients that approach palliative care department of our institution for pain management.

Keywords: palliative care; Pain management; Urological cancer

Introduction

Urinary carcinoma progresses and causes persistent and disabling pain in patients. On average, 40–80% of all patients with urological cancer in the terminal phase experience pain [1]. Most patients benefit from basic concepts of analgesia, including the measuring and documenting of pain scores at the bedside. However, pain is often poorly managed by clinicians, with approximately 50% of patients receiving inadequate analgesia [2-4]. Pain needs to be diagnosed based on the patient's clinical condition and the specific type of cancer. In particular, the characteristic of urological cancer-related pain varies. Moreover, pain from cancer can be more complex than that of surgery. Furthermore, pain from acute renal obstruction varies in intensity and duration. Pain mitigation and therapy is one of the most important primary medical tasks of the urologist. Hence, analgesic therapy would be tailored as per the requirements of the individual patient. In the case of neuropathic pain, treatment with opioids alone has limited efficacy and thus it should be administered with analgesics. In addition, invasive analgesic therapies should occasionally be considered. Neuropathic pain often requires expert's assistance in managing the pain.

The following features of pain management techniques are used in urological cancer: (1) Oral medication as a preemptive drug in many cases indicates that oral intake is possible until the terminal phase of urological cancer. (2) Renal function, which is responsible for drug metabolism, is often compromised. This review aimed at providing an overview of the pain management techniques adapted to the urological cancer patients under the palliative care. In addition, the article analyzes the urological cancer patients who were referred to the palliative care department of our institution for pain management.

Pathophysiological Mechanism of Urological Cancer-Related Pain

The perception of pain represents a complex interaction between biological, emotional, and behavioral factors. This review is limited to underlying biological mechanisms while recognizing that psychological factors, which are important in managing postoperative and cancer-related pain. Nociceptors (highly specialized free ends of the sensory nerves) are stimulated by surgical trauma, causing obstructions at the urinary tract leading to inflammation in the urogenital system. Nociceptors are found in skin tissue, muscles, connective tissue, bones and joints (somatic nociceptors), and in viscera (visceral nociceptors) [5,6]. Primary nociceptive impulses travel via A-8 and C-fibers from the periphery to the dorsal horn of the spinal cord, where the first synapses occur. The primary nociceptors enter the dorsal horn of the spinal cord via inter-spinal nerve roots, where they are susceptible to blockade with epidural and spinal local anesthetics at their site of entry (dorsal root entry zone).

The dorsal horn interneuron are modulated via descending impulses from the cerebral cortex and other higher centers in the brain, where perispinal opioids, α-adrenergic agents, neostigmine, and N-methyl-D-aspartate agonists have modulating effects on the transmission of pain. From the dorsal horn, secondary neurons intersect across the midline and ascend via the medial and lateral spinothalamic tracts to the thalamus. From the thalamus, nociceptive information is transmitted to the cerebral cortex. Impulse processing (either inhibitory or excitatory) occurs at each level of this pathway, generating pain. The

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nature, intensity, and the character of the Pain (e.g., burning, twinging, twitching, and oppressive) may vary with the change in the location. This pain generates spinal reflexes, which in turn increases the fasciated and smooth muscle tone. Strong pain increases sympathetic tone, resulting in tachycardia and arterial hypertension. Other pain-related vegetative symptoms such as nausea and vomiting can occur, along with depression, anxiety, insomnia, irritability, and other mood and behavioral effects [7]. These biological mechanisms show no defined correlation between stimulus and response. Tissue that is traumatized from inflammation or surgical interventions liberates mediators of inflammation, such as bradykinins, prostaglandins (PGs), and cytokines [8]. These substances decrease the specific threshold of the nociceptor neuron [9]. Consequently, the flow of afferent impulses to the spinal cord is intensified, thus resulting in primary hyperalgesia. For example, painful stimuli in the area of the nociceptor will be sensed as more intense than it would normally be [10]. Anti-inflammatory agents such as steroids and nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effects at this peripheral site. In addition to this "protective function," a permanent peripheral flow causes changes in the central nervous system (CNS). There is an evidence of different mechanisms, including increased expression of excitatory N-methyl-D-aspartate-receptors, immediate early gene expression, and increased Ca2+ release, that contribute to this change. This is summarized as the sensitization of the spinal cord [9]. This sensitization causes a lower threshold for switching the peripheral stimulus to the second neuron in the dorsal horn. Electroencephalographic methods show amplified impulses, even after removing the noxious stimulus. This extension of pain with time is referred to as long-term potentiation [11]. Moreover, the receptive area of the spinal neuron becomes enlarged, such that pain is perceived even in untraumatized, lesion-associated regions. This extension of pain with the site is termed as secondary hyperalgesia. Long-term potentiation and hyperalgesia indicate the plasticity of the CNS during both acute and chronic pain states. As a result of the peripheral and central plasticity, pain gets intensified and turns more difficult to treat. These changes contribute to the poor success rate of the treatment [12], albeit that psychological factors are also important in the transition from acute to chronic pain [13]. Therefore, effective measures to relive pain during at this acute state may prevent chronic pain development.

Quantitative Measurement of Pain

Pain is a subjective symptom; therefore, the basis of pain measurement is the self-assessment of pain intensity by the patient. Pain intensity should be specifically elicited from the patient during rounds or in the clinical setting. Giving a numerical score to pain intensity allows physicians and nurses to communicate with the patient about the pain and to judge the efficacy of analgesic therapies. Therefore, the measurement and documentation of pain is an essential component of pain therapy. The Numerical Rating Scale (NRS), which measures pain intensity, is used to measure the efficacy of pain treatment, and its use should be standard in clinical practice [14]. The NRS ranges from 0 to 10, where "10" represents the maximum conceivable pain and "0" represents no pain. A value between 0 and 3 is regarded as normal or acceptable, and many researchers considered a score ≥ 4 as painful that must be subjected to treatment. A single recording of pain intensity when the patient is in a resting position is not recommended. Pain should be assessed during mobilization, respiration, or physiotherapy. Relevant conditional function restrictions due to pain should be preferentially assessed and treated [14]. Examinations such as endoscopies or punctures can cause additional pain and should be considered in pain management concepts. Documenting pain scores plays a key role in providing adequate and timely treatment; the scores are documented on the patients' chart so that a temporal correlation is transparent. During ward rounds, pain scores are interpreted, and if required, pain therapy is adjusted. The aim of pain therapy is not to eliminate pain but to reduce the pain level to make it bearable and thereby prevent functional impairment.

Pain Management

The World Health Organization (WHO) developed a 3-step analgesic "ladder" to provide a framework for pain relief, which is currently used for pain management for cancer patients. The WHO's Pain Relief Ladder recommends that non-opioid analgesics should be used as the first step, followed by weak opioids for mild to moderate pain, and if pain persists or increases, patients may be treated with strong opioids until they are pain-free. The most common non-opioid analgesics are acetaminophen and NSAIDs [15]. Within the category of opioid analgesics, weak opioids include drugs such as tramadol, dihydrocodeine, and codeine, and the most frequently used strong opioids include morphine, fentanyl, oxycodone, buprenorphine, hydromorphone, methadone, and tapentadol [16]. Coanalgesics, or adjuvant analgesics, may also be administered to calm fear and anxiety. As an example of coanalgesic use, opioids may be administered together with NSAIDs, glucocorticoids, and bisphosphonates for the patients with bone pain [16].

In addition to tumor-specific therapy, palliative-analgesic therapy should also be considered for the cancer patients. Pain therapy should be considered for the patients with complications such as pathological fractures, obstructions, or bleeding. This is possible through tumor-specific procedures such as radiotherapy, radioisotope therapy, chemotherapy, hormone therapy, and surgery. Physiotherapy can also be helpful. The side effects of therapeutic measures must be evaluated. Only the patient can decide which side effects are acceptable.

Pharmacotherapy

Non-opioid analgesics

The underlying mechanism of pain is an important consideration in the selection of a non-opioid analgesic. Anti-inflammatory drugs such as metamizole are preferred for the treatment of visceral pain. Practitioners must carefully consider various options to be used to reduce the pain among the patients. The first and the foremost criteria should be to minimize the possible side-effects to provide this short-term benefit. Intravenous or oral non-opioid analgesics should be combined with the titration of fast-acting opioids as per requirement without regional analgesia. The gastrointestinal, nephrotoxic, and cardiovascular side effects that occur with the use of NSAR or selective cyclooxygenase 2 (COX-2) inhibitors should be carefully evaluated. Drugs with the lowest cardiovascular risk such as Naproxen, ibuprofen, and celecoxib should be considered to avoid risk factors, [17].

Opioids

The use of opioids rarely induces psychological dependence; however, physical dependence is common with the chronic use of this type of drug. For this reason, the dose is systematically reduced in the discontinuation of opioid therapy. The most frequent adverse effects of opioid use are gastrointestinal dysmotility, nausea, and sedation. Prolonged prophylactic treatment should be given for constipation. Up to 40% of patients experience nausea and vomiting in the first few days of therapy, which can be temporarily treated with anti-emetics [18]. The efficacy and side effects of various opioids are very similar, but pharmacokinetic differences exist with the various drugs. Constipation

occurs less frequently with transdermal opioid application than with oral administration. The dysmotility of the gastrointestinal tract caused by opioids can be treated with an opioid antagonist such as Naloxone. These drugs must be administered orally if this combination is not effective. In the case of an inadequate action–side effect relationship, a unique opioid rotation can be considered. Fast-setting free galenicals are used for the treatment of severe pain and single dose of opioids amount to approximately one-eighth to one-sixth of the daily dose. Reducing the opioids dosage is one of the most frequent mistakes in tumor pain therapy. In cases of acute, severe pain, fast-acting preparations such as oral morphine tablets or drops, fentanyl pills, or nose spray can be used. These compounds are absorbed orally or through the mucus or skin, and characterized by their fast onset and short duration of action. Oral slow-release opioids are increasingly used in systemic pain management despite little evidence of their efficacy.

Steroids

The use of steroids is based on their antiphlogistic and anti-edematous effects. Steroids are widely used in the case of elevated intracranial pressure, nerve plexus infiltration, spinal cord compression, and liver capsule tension. Additional desired effects with the steroids include appetite stimulation, central antiemetic effects, prevention of drug-induced nausea, and mood elucidation. High dose of corticosteroids are prescribed only for short term uses due to its adverse effects in the long run. In a palliative situation, these issues are considered to be relative.

Other therapies

Prior to invasive procedures, therapy with an NMDA-receptor antagonist such as ketamine should be considered, as it has proven efficacy against opioid tolerance. NMDA-antagonist mechanisms are also believed to be involved in the action of the opioid L-methadone. Although individual reaction to it varies, a steady state can be reached only after 4–7 days. Bisphosphonates delay osteoclast activity and are indicated in cases of osteolytic metastases. Hence, the use of nonretarded preparations should be avoided. Neuropathic pain therapy is based primarily on the use of antiepileptic drugs and certain antidepressants, with opioids administered as second-line therapy. Another possible treatment involves the topical application of lidocaine or capsaicin without fail in cases of superficial neuropathic pain. Topical therapy with a lidocaine patch is used for patients with post-therpetic neuralgia.

Non-pharmacotherapy

Pharmacotherapy alone is insufficient to treat chronic pain. Physiotherapy, psychological therapy, and complementary procedures (e.g., transcutaneous electrical nerve stimulation and acupuncture) are important components of an interdisciplinary multidimensional pain therapy. Patients with a chronic pain are generally advised to attend interdisciplinary pain reduction conferences, in which further diagnostic and therapeutic options are discussed. Neurosurgical procedures such as regional field stimulation or spinal cord stimulation can be considered for the treatment of different neuropathic pain syndromes.

Team Approach

The European Association of Urology guidelines concerning pain control in urology recommends a multidisciplinary team approach for the treatment of pain in the urinary organ region. The summary of the section on pain control in the 2010 edition of the guideline was created by a panel consisting of multidisciplinary specialists and was based on an inclusive review of studies from 2000 to 2010. This report indicated that multidisciplinary teams provide more effective palliative care. Unfortunately, the necessity of a team-care approach for cancer patients has not been fully recognized in Japan [19]. Although pharmacotherapy is usually used for pain control, Physiotherapy, psychosocial and psychiatric support is essential in the palliative care of patients. The primary goal of a pain clinic is to address these psychosocial and medical issues through a multidisciplinary approach [20]. Therefore, a multidisciplinary team of experts is needed for etiology-specific pain management and therapeutics [21]. These patients often benefit from multimodal, interdisciplinary pain management comprising psychological and educational approaches combined with physiotherapy.

Pain Therapy for Renal Colic

Pain in the prostate cancer occurs in the early and advanced stages. Patient may tolerate the pain in the early stages, as it is nominal. In the advanced cases, there might be Pain directly by the cancer (77%), due to cancer treatment (19%), or unrelated to either (3%) [23]. Therefore, pain management must focus on the symptomatic patients with metastases. The overall incidence of chronic pain among patients with prostate cancer is approximately 30–50%, but as patients enter the terminal phase of their illness, this figure increases up to 90% [24]. Pain may be directly attributabted to growth of tumor in three main areas, which include tumor infiltration to bone, nerve, or a hollow viscous. In cases of prostate cancer, visceral pain may occur when the tumor invades the surrounding organs of the prostatic gland. Neuropathic pain develops at the perinea and anal areas when the tumor invades the surrounding nerves. In addition, lymph flow would be cut off due to metastasis at the lymph nodes in the pelvis, causing somatic pain and edema of the lower limbs. Overall, 80% of advanced prostate cancers cause bone metastasis and somatic pain. Furthermore, neuropathic pain develops if the nerves are compressed by bone metastasis and tumor invasion. Urothelial cancer is a common cancer and transitional cell carcinoma (TCC) is the most frequent cancer of the bladder and upper urinary tract [25]. It arises much more frequently in the bladder than in the collecting system (calices, renal pelvis, and ureter). From the perspective of pain, TCC and other histotypes of urothelial malignant tumors do not differ. In bladder carcinoma, pain can be present throughout the history of the disease (occurring early as a burning pain together with irritating symptoms or late in the advanced disease due to local invasion of neighboring tissues or metastatic organ invasion). TCC of the renal collecting system represents 5-10% of all kidney tumors and 5% of all TCC of the urinary tract [26]. TCC of the ureter accounts for only 3% of all TCC [27]. In TCC of the upper urinary tract, pain is an initial symptom in approximately 30% of cases. Bladder bleeding occurs in urological cancer as a result of tumor bleeding or blood coagulation disorders, causing visceral pain and tumor progression to spread into organs surrounding the bladder. These results in pain mixed with somatalgia, caused by movement disorder or inflammation of the bladder mucosa. Renal cell carcinoma is mainly diagnosed incidentally. We believe that renal cell carcinoma causes pain only when the tumor invades the surrounding areas or obstructs the outflow of urine owing to hemorrhage and subsequent formation of blood clots. 20% - 30% of patients present with metastatic disease, and 30% of patients with localized kidney tumor develop metastases during follow-up. Thus, 50–60% of all patients with renal cell carcinoma develops metastases during their life and may require treatment due to the presence of symptoms, mainly pain. Renal cell carcinoma spreads mainly to the lung, bone, brain, liver, and ipsilateral or contralateral adrenergic glands. Patients with metastases have a maximal 2-year survival rate and 20% of cases undergo palliative treatment. In cases of kidney

cancer, the extension of the renal capsule would cause visceral pain that is accompanied by the enlargement of the tumor itself and urinary tract obstruction. Neuropathic pain occurs if the kidney cancer invades the retroperitoneal nerves. Somatic pain control is challenging as it easily metastasizes to the lungs, bones, and lymph nodes. The penile lesion itself usually alerts the patient the presence of a penile cancer, which in most cases occurs on the glans (48%) and prepuce (21%). Patients with penile cancer seem to delay seeking medical attention because of embarrassment, guilt, fear, ignorance, and neglect. This level of denial is substantial given that the penis is observed and handled daily. Pain does not develop in proportion to the extent of the local tumor and is not usually a presenting complaint [28]. Till date, there has been no consensus on the therapeutic management of metastatic, and only few controlled studies have been investigated with penile carcinoma and related pain and obtained significant statistical results.

Acute urinary tract obstruction induces intensive visceral nociception from increased tension in the renal pelvis and ureteric wall, secondary to increased intraluminal pressure. Renal colic is characterized by an abrupt onset of unbearable pain, whereas other (chronic) urinary tract obstructions may be associated with less intense pain. Because of the increasing pressure, the impulse rate of the nociceptors is accelerated. The concentration of nociceptive mediators increases and the nociceptors that were formerly inactive become active [9,10]. In addition, smooth muscle ischemia might occur and activate more nociceptors. Pain therapy aims to reduce mediator release and reduce smooth muscle tone in such cases. The previous standard treatment of severe pain consisted of parenteral opioids; as these patients often experience nausea; oral opioids are not as effective. In addition, parenteral opioids resulted in almost immediate induction of analgesia. Frequently, a drawback to opioids is aggravation of nausea and vomiting. Since the introduction of ketorolac, a parenteral NSAID, the therapy for renal colic has changed. Availability of parenteral COX-2 inhibitors may enhance the usefulness of NSAIDs for treating renal colic in future. Recently, a meta-analysis by Labrecque et al. [29] showed that NSAIDs and opioids have equal effectiveness in reducing colic pain. A double-blind comparison of parenteral ketorolac and pethidine showed that they were equally effective in reducing the pain of renal colic with minimized adverse effects [30]. Through the inhibition of COX-2, NSAIDs reduce the production of nociceptive mediators. Acute ureteric obstruction leads to increased renal PG release in the initial phase; this mediates an increase in renal blood flow (RBF) and diuresis with rising pressure. Thus, NSAIDs can reduce RBF and diuresis because of their COX-inhibiting properties. In summary, these effects are beneficial for pain management but may be detrimental for renal function. Although healthy individuals may be able to tolerate reduced RBF effectively, patients with preexisting renal or severe atherosclerotic disease are in danger of developing acute renal failure after the administration of NSAIDs [31]. Before administering NSAIDs, the physician should carefully consider the renal function status of the patient [8]. Desmopressin may become an alternative to opioids in the treatment of renal colic pain in future. This synthetic vasopressin analogue is known to have antidiuretic effects, and it may relax smooth muscle tone. A recent report showed equal analgesic potencies of desmopressin and diclofenac in patients with acute renal colic [32]. The study underlines the need for further investigation to determine the role of opioids, NSAIDs, and desmopressin in treating renal colic [33].

Pain from Urogenital Tumors

Renal or prostate neoplasms frequently metastasize to bone (e.g., spine, pelvis, and skull), and such bone metastases are associated with pathological fractures, hypercalcemia, and neurological deficits, leading to a substantial impairment of quality of life. The liberation of pain-provoking substances in the tissue, microfractures, periosteal tension caused by increasing pressure, and neural compression with pain and/or paralysis (neuropathic pain) are particular challenges of neoplastic bone invasion. The patient's complaints may not always correlate with diagnostic findings, and every metastatic event does not cause pain [34]. Pain caused by bone metastases is nociceptive pain but can become complicated with neuropathic pain if the tumor invades or compresses a nerve, neural plexus, or spinal cord. Combinations of nociceptive and neuropathic pain are common in such cases. In a large population of patients with different types of cancer, one-third of the patients with tumor-related pain were affected by neuropathic pain components [35]. The diagnosis and recognition of neuropathic pain is important because it is associated with therapeutic consequences in the choice of the analgesic technique. Nociceptive pain is well localized; initially, it correlates with physical strain and then also occurs at rest. Neuropathic pain frequently has a constant "burning" character. Further sensory disturbances might occur, such as paresthesia (tingling), allodynia, hyperalgesia, and intensive lancing pain that radiates into the area of the affected peripheral nerve or root. Some patients with neuropathic pain from tumor compression of a nerve or nerve plexus will present with escalating pain, requiring increasing opioid doses, which may occasionally be several fold over a few days. The efficacy of opioids is diminished in neuropathic pain; hence, additional coanalgesics are necessary [36]. At this point, consultation with a specialist in pain management is often helpful. Oncological neuropathic pain syndromes are some of the most challenging cases that a pain management physician will encounter. Therefore, recognition of the syndrome is of paramount importance [36-38]. The impaired activity of patients with severe neuropathic pain represents an enormous strain; psychological changes frequently occur and specific therapeutic intervention is required. The WHO recommends a stepwise scheme for the treatment of cancer pain syndromes (and for neoplastic bone pain). A stepwise scheme uses additive or perhaps synergistic effects of different substances. Non-opioid coanalgesics are not listed in this WHO scheme, but they are essential and can improve opioid effects in antinociceptive therapy [39]. Bisphosphonates and calcitonin are helpful for stabilizing bone metabolism. Epidural and intrathecal opioids are occasionally useful in managing bone pain from metastases. Nerve destruction by intrathecal or epidural phenol is occasionally useful for selected patients with neuropathic pain, and has the advantage of long-term benefits from a single injection [40]. The risks of perispinal neurolytic blocks include motor and sensory functional loss of the extremities, and loss of bowel and bladder functions. The physician should balance the risk-to-benefit ratio for each patient with experience in these techniques, after discussion with the patient and patient's family. In some circumstances such as in patients with poorly controlled oncological pain and those confined to bed, the bowel and bladder functions may already be lost and a perispinal neurolytic block may seem acceptable to the patients considering the deteriorated condition.

Urological Cancer Patients Referred to the Palliative Care Department of Our Institution

The Department of Palliative Medicine, National Cancer Center Hospital, Japan, was established to provide palliative care services. Physicians refer approximately 300 inpatients to the palliative care department annually for pain management.

Patients that enrolled between April 2009 and March 2010 and treated at our institution are considered for the present study. We

analyzed the urological cancer cases in patients who were referred to the palliative care department for the management of pain and evaluated the measures taken, with a focus on clinical practice. After a detailed medical examination by interviewing and obtaining physical findings for each patient, the palliative care team initiated the pain management therapy. After the medical examination, we examined the patients' computed tomographic and magnetic resonance imaging findings. A dermatome or osteotome was used to obtain samples for pathophysiological diagnosis. We administered treatment on the basis of the patient's pharmacological regimen and supportive care knowledge. Physiotherapy was an integral part of treatment and used the NRS for pain assessment. A decrease of ≥ 2 points was considered representative of significant amelioration.

Demographic data (e.g., age and sex), primary cancer lesion, stage (determined by the American Joint Committee on Cancer/International Union against Cancer TNM classification and stage grouping), and metastasis etc were analyzed using the computerized database and the medical records.

We have evaluated the prior use of analgesics (opioid analgesics, non-opioid analgesics, and analgesic adjuvants) at the time of referral to the palliative care department, diagnosis of pain by the palliative care department, and initial interventions for cancer pain, including pharmacotherapies and non-pharmacological therapies.

The study was limited to 48 treated cases referred to the palliative care department by the urological division of our hospital (male/female: 33/15). The median age of the patients was 60.31 ± 12.78 years (range: 30-82 years). The most common urological cancer was bladder cancer, which was found in 16 patients (33.3%), followed by renal cell carcinoma in 10 patients (20.8%), TCC of the renal pelvis in 7 patients (14.6%), and prostate cancer in 6 patients (12.5%). The recurrence rate was 45.8%, and 43.1% of the patients had clinical stage IV cancer. Forty-three patients had metastasis (Table 1). The most common site of metastasis was the bone, which was found in 29 patients (60.4%), followed by lung metastasis in 19 patients (39.5%), brain metastasis in 15 patients (31.2%), dissemination in 11 patients (22.9%), and lymph node metastasis in 11 patients (22.9%; Table 2). Forty-five of 48 patients (93.7%) received preemptive analgesia at the urology department before intervention by the palliative care department. With regard to route of administration, 39 (86.7%) of 45 patients received analgesics orally, and the remaining 6 patients (13.3%) received analgesics parenterally. Analgesics used prior to referral to the palliative care department included opioids for moderate to severe pain (morphine, fentanyl, and oxycodone; 38/48: 79.1%), non-opioid analgesics (NSAIDs and acetaminophen; 43/48: 89.5%), and analgesic adjuvants (15/48: 31.2%). Among the 38 patients who received preemptive opioids, 29 (76.3%), 6 (15.7%), and 4 patients (10.5%) were treated with oxycodone, fentanyl, and morphine preparations, respectively. NSAIDs were used in 38 (88.3%) of the 43 patients who had received preemptive non-opioid analgesia, and 50% of the prescribed NSAIDs were not selective COX-2 inhibitors. Among the 15 patients who received preemptive adjuvant analgesic therapy, anticonvulsants were most commonly used in 10 patients (66.6%; Table 3). In the diagnosis of urological cancer-related pain in the patients who were referred to the palliative care department, somatic pain was the most common and found in 38 patients (79.0%), followed by neurogenic pain in 31 patients (64.5%) and visceral pain in 13 patients (27.0%; Table 4). Multiple causes of pain were diagnosed in 22 of the 48 patients. Initial interventions for cancer pain included increased quantity of oxycodone (22.9%), introduction of oxycodone (12.5%), introduction of anticonvulsants (10.4%), and change in the type of NSAID (10.4%; Table 5). Most of the changes

Sex	(n = 48)	n (%)
Male	33	(68.8)
Female	15	(31.3)
Age		
Mean ± SD	60.31 ± 12.78	
Range	30 - 82	
Primary lesion of cancer		
Bladder cancer	16	(33.3)
Renal cell carcinoma	10	(20.8)
Transitional cell cancer of the renal pelvis and ureter	7	(14.6)
Prostate cancer	6	(12.5)
Retroperitoneal malignant tumor	5	(10.4)
Testicular cancer	2	(4.2)
Bladder cancer and renal cell carcinoma	1	(2.1)
Bladder cancer and prostate cancer	1	(2.1)
Stage		
I	2	(4.2)
II	1	(2.1)
III	2	(4.2)
IV	21	(43.1)
Recurrence	22	(45.8)
Distant metastasis		
-	5	(10.4)
+	43	(88.8)
Previous surgery		
-	24	(50.0)
+	24	(50.0)
Previous chemotherapy		
-	31	(64.6)
+	17	(35.4)
Previous or even current therapy with bisphosphonates		
-	21	(43.8)
+	27	(57.2)

Table 1: Patient characteristics

in the type of NSAID used consisted of replacing a selective COX-2 inhibitor with another NSAID. Other interventions included physical supportive therapies such as the use of an orthopedic corset (10.4%), consultation with a psychiatrist (8.3%), administration of epidural blocks and other nerve blocks (6.3%), radiotherapy, acupuncture, and moxibustion (2.1% each). At the time of intervention in the palliative care department, disturbance of consciousness/delirium was observed in 50% of the patients who were receiving morphine. In addition, respiratory depression and delirium/disturbance were observed in 33.3% of the patients who were receiving fentanyl. Among the patients using oxycodone, respiratory depression and delirium/disturbance of consciousness were observed in 10.3% and 13.7%, respectively. Among the patients who experienced respiratory depression, 50% underwent opioid rotation to fentanyl preparation, with the remaining 50% receiving oxycodone and fentanyl preparation dose reductions (25% each). Among the patients with delirium/disturbance of consciousness, 75% and 25% underwent opioid rotation to fentanyl preparation and oxycodone, respectively. Psychiatric intervention was performed in all the patients who experienced delirium. The overall pain improvement rate with these interventions was 93.7%.

In most cases, the patients had disease recurrence and stage IV cancer. In addition, many cases had distal metastasis, especially bone metastasis and as many as 93.7% of the patients received preemptive analgesia at the urology department. These results have clarified that

Site of metastasis		n (%)
Bone	29	(60.4)
Lung	19	(39.5)
Brain	15	(31.2)
Dissemination	11	(22.9)
Lymph node	11	(22.9)
Liver	6	(12.5)
Adrenal gland	2	(4.1)
Local	2	(4.1)
Kidney	1	(2.0)
Others	4	(8.3)

Table 2: Details of metastasis

Analgesics		n (%)
Opioid analgesics	38	(100)
Morphine	4	(10.5)
Fentanyl	6	(15.7)
Oxycodone	29	(76.3)
Non-opioid analgesics	43	(100)
NSAIDs	38	(88.3)
NSAIDs and Acetaminophen	5	(11.6)
Analgesic adjuvants	15	(100)
Anticonvulsant	10	(66.6)
Steroid	2	(13.3)
Anticonvulsant and antide-pressant	2	(13.3)
Anticonvulsant and steroid	1	(6.6)

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

Table 3. Details of prior analgesics

Types of pain		n (%)
Somatic pain	38	(79.0)
Neurogenic pain	31	(64.5)
Visceral pain	13	(27.0)

Table 4: Diagnosis of pain

Analgesics		n (%)
Opioid analgesics		
Increased quantity of oxycodone	11	(22.9)
Introduction of oxycodone	6	(12.5)
Increased quantity of morphine	3	(6.2)
Change to fentanyl (introduction of opioid rotation)	2	(4.1)
Introduction of morphine	1	(2.0)
Increased quantity of fentanyl	1	(2.0)
Non-opioid analgesics		
Change in type of NSAIDs	5	(10.4)
Introduction of NSAIDs	4	(8.3)
Introduction of acetaminophen	2	(4.1)
Increased quantity of NSAIDs	1	(2.0)
Analgesic adjuvants		
Introduction of anticonvulsant	5	(10.4)
Introduction of steroid	4	(8.3)
Increased quantity of anticonvulsant	1	(2.0)
Introduction of antidepressant	1	(2.0)
Decreased quantity of antidepressant	1	(2.0)
Increased quantity of anticonvulsant and introduction of steroid	1	(2.0)

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

Table 5: Initial pharmacotherapeutic interventions for cancer pain

pain management in the field of urology in our hospital is initiated by the urologists. Many patients who were referred to the palliative care department were diagnosed with somatic or neuropathic pain. Therefore, many of the cases were recurrent, advanced cancers, and it can be assumed that the patients were referred to the palliative care department for the treatment of pain associated with the advanced progression or distal metastasis of the original tumor.

The use of oral medication as a preemptive drug in many cases indicates that oral intake is possible until the terminal phase of urological cancer. We found that the usage of analgesic adjuvants for preemptive analgesia was relatively less frequent than that of opioids and non-opioid preparations. Among the opioid preparations administered preemptively, oxycodone was used most frequently and morphine was used least frequently. Morphine can be administered through various routes such as orally (quick- and sustained-release preparations), and via intravenous, subcutaneous, and transrectal injections. However, in cases of renal dysfunction, active metabolites (M-6-G) with an opioid effect are likely to accumulate and cause somnolence or respiratory depression. Many urologists are aware of this possibility, and therefore frequently use oxycodone, the metabolites of which have almost no opioid effect. However, the expertise of palliative care physicians would be required when a favorable analgesic effect cannot be obtained after the introduction of oxycodone. The most frequent opioid intervention performed by the palliative care department was to increase the amount of oxycodone at the appropriate dosage/frequency as determined by the palliative care specialists. In addition, few patients experienced adverse effects of opioid use. In such cases, the palliative care physicians changed the treatment by opioid rotation. Several cases are referred to the palliative care department, including cases of inadequate pain management or uncontrollable adverse effects after the initiation of opioid therapy at the urology department. Thus, efforts to optimize opioid therapy are ongoing.

Of the non-opioid drugs, NSAIDs were used most frequently for preemptive analgesia. Among the NSAIDs administered preemptively, 50% were selective COX-2 inhibitors. The adverse effects of NSAIDs include renal dysfunction, gastrointestinal ulceration, and decreased platelet function. All of these adverse effects occur when the production of PGs or thromboxanes is decreased as a result of COX inhibition. Selective COX-2 inhibitors were developed to minimize the adverse effects of NSAIDs. In this study, renal dysfunction occurred as a result of NSAID use; therefore, a shift to a selective COX-2 inhibitor was the most frequent intervention. NSAIDs can be used safely and effectively as an option for pain management in terminal cases of urological cancer by the palliative care department and by urological physicians who are well experienced in the management of renal function. The use of preemptive analgesic adjuvants in the urology department was less frequent than that of other opioid/non-opioid drugs. However, among the preemptive drugs, anticonvulsants were the most frequently used analgesic adjuvants. Anticonvulsants were also most frequently used as analgesic adjuvant at the palliative care department. Anticonvulsants were used for the management of neuropathic pain caused by cancer progression. In addition to painkillers, epidural anesthesia and nerve block were also utilized by the palliative care department. The WHO recommends a stepwise scheme for the treatment of cancer pain syndromes and neoplastic bone pain. Epidural and intrathecal opioids are occasionally useful in managing bone pain caused by metastases. Nerve destruction by intrathecal or epidural phenol is occasionally useful in selected patients with neuropathic pain [40]. In addition, the palliative care department conducts consultations for the departments of orthopedics, psychiatry, and radiology. Pain is a complex experience

comprising physiological, sensory, affective, cognitive, and behavioral components. An individual's perception of pain intensity is associated with the interactions between physical, psychological, cultural, and spiritual factors [20]. Although pain control is crucial to any effort at relieving suffering, and pain and suffering are closely related, they are nevertheless distinct.

Conclusion

The use of oral medication as a preemptive drug in many cases indicates that oral intake is possible until the terminal phase of urological cancer. Pain management in the field of urology in our hospital is initiated by urologists. Several cases of urological cancer are referred to the palliative care department of our hospital, including cases of inadequate pain management or uncontrollable adverse effects after the initiation of opioid therapy at the urology department. In addition, the palliative care department conducts consultations for the departments of orthopedics, psychiatry, and radiology. Therefore, a multidisciplinary team of experts is needed for etiology-specific pain management and therapeutics. Patients often benefit from multimodal, interdisciplinary pain management comprising psychological and educational approaches, as well as physiotherapy.

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