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Reviews

Management of Orofacial Pain in Cancer Patients

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Pain in patients with cancer may arise due to the primary disease, or due to therapy of the malignant disease. Pain may be caused by oral infection, oral mucositis, and by alteration in musculoskeletal and neurological function. The management of orofacial and oropharyngeal pain in patients with cancer is reviewed in this paper.

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INTRODUCTION

PAIN FROM cancer or cancer treatment is a major concern of patients and health care professionals. It seriously erodes the quality of life and can complicate the course of cancer treatment. Head and neck and oral pain can arise from the primary tumour, metastases, or from local infiltration by cells of a haematological malignancy. Pain due to cancer therapy is common and can represent either direct toxicity or delayed complications of therapy. In spite of the importance of pain in head and neck cancer there is limited information on the incidence and the severity and type of orofacial/oropharyngeal pain in cancer patients [1–3]. This paper will review the management of pain in the oral cavity and head and neck region during and following cancer therapy.

ORAL INFECTION

Since oral infection can significantly complicate cancer therapy, frequently causing local pain, and may lead to systemic infection in immunocompromised conditions, patients should be evaluated for dental and periodontal disease before the initiation of cancer therapy. Maintaining good oral hygiene in addition to decreasing the risk of local infection may reduce oral mucositis reducing the risk of systemic infection [4–9]. Elimination of dental disease is critical for patients who will receive radical radiation therapy that includes the dentition within the high dose volume because of the risk of long-term complications of osteoradionecrosis if surgical treatment is required [10, 11].

Gingival and periodontal disease has been shown to be a potential cause of systemic infection in immunocompromised patients [4, 6, 12–14]. Shifts in the oral flora may occur due to the overgrowth of opportunistic pathogens or nosocomial organisms or emergence of organisms resistant to the antibiotics usually chosen for oral infection [6, 15–18]. Infections of the oral mucosa and perioral skin occur frequently and may complicate oral mucositis.

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Patients with moderate to severe periodontal disease may require extraction, if the teeth will be included in the high dose radiation treatment volume, or in a patient who will become neutropenic. Therefore, the dental evaluation should be conducted early in the radiation therapy treatment planning, so that appropriate dental care can be completed and healing can occur prior to the start of the radiation. Clinical diagnosis of endodontic or periodontal disease in immunocompromised patients may be more difficult due to the reduction in the inflammatory response which can reduce the overt signs and symptoms of infection and inflammation [16, 19].

Teeth with symptomatic periapical pathosis should be treated by pulpectomy or extraction. If surgical dental treatment is contra-indicated because of the cancer or its treatment, palliation with appropriate endodontic therapy, antibiotics and analgesics should be instituted until definitive therapy is possible [4, 13, 14, 20].

Topical antimicrobials

The use of topical antimicrobial agents to manage periodontal infections as well as to prevent oral bacterial and fungal colonisation and infection requires further study [21–35]. Topical nystatin rinse has been disappointing in its ability to prevent fungal colonisation and in preventing subsequent infections in neutropenic patients[21, 24–26, 35]. In patients who receive radiation therapy the most common mucosal infection is candidiasis. A number of factors increase the risk of oral candidiasis including changes in oral flora, antibiotic use, decreased immune function, and xerostomia [36–39]. Patients can become colonised and clinical infection can continue in the face of continuing xerostomia [37–39].

Chlorhexidine has been reported to be useful in the management of bacterial infections in immunocompromised patients [28, 40, 41]. Reduction in the oral bacterial flora, candida colonisation and oropharyngeal candidiasis has been reported in several papers [22, 26, 28, 29, 31, 33–35, 42–47].

Chlorhexidine has been reported to result in improved gingival health, and reduce mucositis by some authors [22, 29] however, this has not been confirmed in other studies [23, 30, 32, 33, 35]. Candida may be suppressed by chlorhexidine in patients receiving head and neck radiation therapy [48]. Selective elimination by topical antibiotics of gram-negative

bacteria has been reported to reduce the incidence and severity of ulcerative mucositis in radiation therapy, and that candida was not shown to be associated with ulcerative mucositis [48]. Whether the secondary damage caused by gram-negative oral flora plays a central role in the development of ulcerative mucositis in radiation therapy requires further study, as the principle toxicity has been felt to be the direct tissue toxic effects of the radiation.

Increased gram-negative colonisation of the oral cavity has been reported associated with chronic use of chlorhexidine in patients with leukaemia and patients receiving a bone marrow transplant (BMT), however, there has been no evidence to date that this shift in the oral flora has led to clinical infection [22, 46]. The lack of significance of gram-negative colonisation of the oral cavity in these settings may be due to broad spectrum antibiotics used in immunosuppressed cancer patients, that are directed at gram-negative organisms. The more recent increase in streptococcal bacteraemia may reflect the effect of the antibiotics in common use in these patients [49]. Thus, the effects of chlorhexidine on streptococci may outweigh the change in oral colonisation by gram-negative organisms due to the broad spectrum antibiotics. However, based upon the report of a correlation between gram-negative colonisation and ulcerative mucositis in radiation therapy [48], this potential relationship requires further investigation.

Systemic antibiotics and antifungals

If an oral infection is suspected, culture and sensitivity is essential in immunocompromised patients. Empiric use of antifungals, antivirals and antibiotics based upon clinical findings is indicated until the results of laboratory testing are available. Guidelines for the use of broad spectrum antibiotics is based upon haematological status, and the presence of fever. In many institutions, antifungals are begun when a patient remains febrile in spite of the use of broad spectrum antibiotics, and in some centres with positive cultures for candida at two or more sites. Topical agents should be used, as their use may add to the effect of systemic agents. Recent reports of suppression of oral candida with prophylactic use of fluconazole are encouraging [50–52].

Reactivation of viral infection is common in myelosuppressed or immunosuppressed patients. A herpes simplex virus (HSV) seropositive patient has a 60–80% risk of virus reactivation during aggressive chemotherapy and bone marrow transplantation for treatment of leukaemia [53–57]. Therefore, prophylaxis of recurrent HSV infection with acyclovir is recommended in seropositive patients during periods of immunosuppression [56,58–61]. Acyclovir is used at high dose in varicella-zoster (VZV) infection, and may be of value in the preventing reactivation of cytomegalovirus (CMV) in patients receiving bone marrow transplantation [62]. However, gancyclovir is the current drug of choice to prevent and treat CMV infections [63,64]. In immunosuppressed patients, topical acyclovir may be used adjunctively with systemic acyclovir to treat reactivated HSV and VZV [58,59,61,65].

MANAGEMENT OF MUCOSITIS AND ORAL DISCOMFORT

The incidence and severity of mucositis has been related to the degree of pre-existing mucosal disease, oral hygiene, and the nature of the cancer treatment [8, 9, 66, 67]. Currently, mucositis pain is managed palliatively until healing occurs. Future directions in prevention and treatment of mucositis may include the use of cytokines (tissue growth factors) and biostimulation of epithelial healing [68, 69]. Bland rinses (0.9% saline solutions with or without sodium bicarbonate), topical anaesthetics, and mucosal coating agents have been suggested but their efficacy has not been subjected to scrutiny by double blind studies [4, 10, 70, 71].

Lidocaine viscous is frequently recommended on clinical grounds. However, the rinse may result in burning sensation when used, and may eliminate the taste sensation reducing the dietary intake. Topical lidocaine has been associated with toxicity including cardiovascular and central nervous system toxicity (seizures); in addition the degree of anaesthesia may increase the risk of loss of the gag reflex and subsequent aspiration [70, 72, 73]. Clinical trials using benzydamine, a topical non-steroidal anti-inflammatory agent, to decrease the pain of oral mucositis, and to prevent mucositis have shown encouraging results [70, 74–76]. Benzydamine produces topical analgesia and transient mild anaesthesia, and may reduce mucosal breakdown due to a stabilisation of cell membranes [75, 77]. Other topical analgesics and anaesthetics may be helpful when they are applied to localised areas or used as a rinse when mucosal involvement is widespread. Systemic agents (see below) may be needed in addition to topical anaesthetic or analgesic agents.

Sucralfate has been used as a cytoprotective agent for gastrointestinal ulcer disease, and preliminary trials have suggested it may be of value in oral mucositis [69, 78,–81]. A double blind trial in paediatric patients did not yield statistically significant reduction in mucositis, but patients experienced less pain and few potential pathogenic microbes were identified on oral culture [81]. Additional controlled studies are required.

MANAGEMENT OF MUSCULOSKELETAL PAIN

Musculoskeletal syndromes are commonly seen in patients with head and neck cancer. The aetiology of dysfunction includes direct effects of the tumour on muscles of mastication and facial expression that limit mandibular movement, bone destruction and fracture. The effects of surgical treatment may be significant if discontinuity of the jaw, or fibrosis of muscles and soft tissue occurs. Radiation fibrosis of muscles and soft tissue and complications of osteoradionecrosis has clearly been shown to affect jaw function [10, 82]. The altered function of the mandible may place stress on the temporomandibular joint or the muscles of mastication, resulting in further dysfunction and pain [83]. Finally, stress, anxiety and depression associated with cancer heighten psychosocial factors that are often associated with temporomandibular disorders (TMD) [82–88].

Management of the pain of mandibular dysfunction may be particularly difficult if discontinuity of the jaw, missing teeth and muscular fibrosis and myofascial pain is present. Treatment of TMD includes care in use of the jaw, physical therapy, mandibular guidance appliances, occlusal appliances, anti-inflammatory agents, analgesics and muscle relaxants [82, 83, 85–90]. Muscle trigger point injections may be helpful in musculoskeletal syndromes. In cancer patients significant derangement in function may occur due to discontinuity of the mandible, major iatrogenic changes in the dentition and occlusion or marked changes in muscle function, and there may be additional considerations in management, that include attempts at rehabilitation of the mandible or the dentition.

The initial treatment of osteoradionecrosis includes maintenance of good oral hygiene, antibiotics to reduce secondary bacterial irritation and appropriate pain management. Control of pain often requires use of systemic analgesics. Resolution of the lesion may require of hyperbaric oxygen therapy and surgery if indicated [11, 92–99]. Therapy including hyperbaric oxygen and surgery has been recommended in symptomatic progressive cases, but a conservative approach has been suggested in asymptomatic non-progressive osteoradionecrosis [11, 99].

NEUROLOGICAL PAIN

Neurologic pain in the head and neck of cancer patients may result from the development of traumatic neuroma, somatic and autonomic collateralisation and/or due to deafferentation following surgery [100]. Neuralgia-like pain can develop following surgical treatment. Aching or burning discomfort may develop between episodes of the electric-like pain.

Diagnostic and therapeutic nerve blocks may be useful in diagnosis and management of oral and maxillofacial pain [101–107]. Local anaesthetic and neurolytic blocks may be useful in localised pain, such as from tumour infiltration. A permanent block is performed only if preceded by a local anaesthetic block that is effective. However, a permanent block may result in a dysesthetic pain [104–106]. Head and neck pain frequently presents with a sympathetic component that produces diffuse burning. A stellate ganglion block may provide diagnostic information and guide the use of phenol injection or sympathectomy. Neurosurgery may have a limited role in squamous cell cancer related pain in the head and neck [88, 102, 104, 108, 109].

Neurological procedures involving surgical and thermal rhizotomy, decompression of the ganglion, alcohol and glycerol injection of the trigeminal ganglion have been discussed [110–112]. Percutaneous radiofrequency trigeminal rhizotomy for treatment of trigeminal involvement due to cancer may be of value in some cases [107–111], however, seldom is the involvement limited to a single nerve in malignant disease [113]. The use of percutaneous radiofrequency procedures of the trigeminal and glossopharyngeal nerve has been suggested as a procedure more easily performed on debilitated patients [107]. Bortoluzzi and Marini [113] have reported pain relief in approximately one-third of patients with phenol injection into cisterna magna in intractable facial pain due to cancer in patients who were not surgical candidates. However it is interesting that no relationship between pain relief and sensory deficit was seen. Difficulties that limit neurosurgical management include the invasive nature of surgery and the frequent extension of pain over several cranial nerves, and the limitation for surgery due to the general health of the patient. However, vertical nucleotomy has been reported to be effective in relieving cancer pain in 3 of 6 patients [112]. In another report, 5 patients who had head and neck malignancies, non-squamous cell carcinoma, were treated with neurosurgical techniques, with successful control of pain for more than 1 year in 3 patients, and improvement in the other 2 [110]. Patients with pain without hypesthesia and dysesthesia may be the most appropriate candidates for surgical procedures [110].

The use of adjunctive techniques in management of neurological pain include transcutaneous electric nerve stimulation and acupuncture [114]. Management of deafferentation pain includes the use of transcutaneous nerve stimulation [114–117], and tricyclic medications (see "central acting medications").

The principle means of management of neurological pain in the head and neck is through the use of medications that may include analgesics, antidepressants, and adjunctive medications.

SYSTEMIC MEDICATIONS IN PAIN MANAGEMENT

Medications used in the treatment of cancer pain may be divided into those directed at the cancer or complication of cancer treatment causing pain, and palliative therapy directed at symptom control. Those that modify the cause of pain include anti-infective, anti-inflammatory, and anti-convulsant drugs. Analgesic drugs elevate the pain threshold. Non-steroidal anti-inflammatory drugs (NSAID) are useful for mild to moderate pain, such as for reducing superficial pain and pain in the musculoskeletal tissues, but they have little effect on visceral pain. The non-steroidal analgesics affect prostaglandin synthesis and reduce the sensitisation of pain receptors. Narcotic analgesics alter perception and reaction to pain, and are used for moderate to severe pain.

The initial analgesic selected should be the least potent analgesic that relieves the pain. With increasing pain, non-narcotic and narcotic agents should be used in combination [118–124]. Analgesics will be more effective and allow a lower total dose when used on a time contingent basis [101–103, 118–123, 125–134]. Drug interactions and the status of liver and kidney function must be considered in the choice of medications and their dose schedules especially for NSAID. Patient controlled analgesia has been shown to provide more effective pain control while reducing the amount of drug required [119, 122, 135, 141]. It has been repeatedly stated that a major problem in analgesic use in cancer patients is the reluctance of health-care workers to provide adequate doses and frequency of medication to effectively control the pain [101–103, 118–122, 125, 135, 142].

Non-narcotic analgesics

Acetylsalicylic acid (ASA), other NSAID and acetominophen may be useful in early stages of cancer pain, and are frequently used in combination with mild narcotics such as codeine [103, 118–124]. Anti-inflammatory analgesics may be of particular value in managing pain caused by tumour involvement of bone, due to the anti-prostaglandin effects of the drug [118, 122]. In patients with thrombocytopenia or conditions causing decreased clotting factors, the use of NSAID must be considered carefully because of the effect of these drugs upon platelet aggregation.

Narcotic analgesics

The primary differences between the agonist narcotics is their length of action and potency. Morphine is the drug of choice for moderate to severe cancer pain [102, 119, 121, 128, 130, 131, 134, 136, 137, 139, 143]. Methadone may provide some advantages including long duration of action and greater solubility than morphine [133, 134]. However, methadone has a tendency to accumulate, which must be considered, particularly in the elderly [119, 122, 139, 144].

Oral administration is desired in outpatient care. However, medications or a route of administration that avoids drug

metabolism in the liver prior to entering the systemic circulation may provide an advantage over those absorbed in the gut [139]. Continuous dosage can be accomplished by intravenous infusion, transdermal administration or indwelling devices (i.e. Infusaid), and intrathecal or epidural injection [122, 136, 145–155]. Intraventricular administration of morphine by subcutaneous pump administration has been reported to provide good pain control with fewer systemic side effects in patients with pain resulting from malignant disease of the oropharynx [156]. Patient controlled analgesia has been reported to result in better pain control in bone marrow transplant (BMT) patients with severe oral mucositis pain and was achieved using lower doses of analgesic [119, 135, 136, 138, 139, 155, 157–159]. Patients with intractable facial pain due to tumour invasion can be provided relief by lumbar epidural morphine when adequate levels of morphine are achieved in the cervical CSF [147, 150, 152, 160]. Sublingual buprenorphine was seen to be effective in outpatient analgesia for patients with head and neck cancer undergoing radiotherapy [161].

The use of narcotics in cancer patients with pain, does not result in difficulties with narcotic addiction [118, 119, 122, 127, 139, 153, 161–167]. While cognitive impairment has been associated with a significant increase in the dose of narcotics, this impairment disappears after 1 week of drug use [168]. Continuous reaction times, pain and sedation scales were compared in patients during chronic oral opioid therapy and epidural opioid therapies, and while no differences were seen in pain control, there was less sedation reported with epidural opioids [169, 170].

Central acting medications

Pain relief has been reported in cancer patients with the use of psychotropic medications [118, 122, 130, 132, 144, 162, 170–178]. The tricyclic antidepressant drugs have been found to have a primary analgesic effect that is distinct from that caused by the narcotic and non-narcotic analgesic drugs [101, 103, 121–123, 125, 162, 171, 178–185]. The tricyclic medications inhibit synaptic re-uptake of neurotransmitters and lead to an increase in serotonin, noradrenalin, dopamine and possibly endogenous opioid levels [43, 44, 121, 130, 144, 162, 171–178, 180, 181, 186]. Analgesic effects are generally achieved at doses lower than those producing antidepressant effects. The psychotropic drugs may act synergistically with other analgesic drugs due to different mechanisms of action, improving sleep, and by altering the emotional state of the patient.

The tricyclics may be also helpful in constant, dysesthetic pain. The side effects of tricyclics include sedation, fluid retention, and dry mouth are generally better tolerated at analgesic doses, however, elderly patients appear to be more susceptible. A medication trial of at least 3 weeks may be necessary to achieve pain relief in some patients [42, 170, 180, 186]. Patients in pain often develop sleep difficulties, and lack of sleep may decrease the pain threshold [42, 187, 188]. Thus the sleep promoting effects of the tricyclics may be of distinct benefit [180, 181]. A study of chronic facial pain in non-cancer patients showed amitriptyline to be superior to placebo in decreasing pain without effect on depression in a non-depressed group [179]. Alprazolam, a benzodiazepine (Xanax, Upjohn Co, Kalamazoo, Michigan) has been shown to be similar to amitriptyline in pain management [189].

Anti-anxiety agents, including the benzodiazepines, may be used to reduce anxiety and as adjuvants in muscular pain and spasm [121, 162, 189]. Steroids reduce inflammation and oedema that may be associated with malignant conditions, and may therefore reduce pain [119]. Steroids may also affect mood, and increase appetite]119, 145]. The primary method of management of neuralgia is the use of anticonvulsant medications such as tegretol or diphenylhydantoin [190–192]. Antibiotic agents may be effective in reducing pain due to infection [193].

BEHAVIORAL APPROACHES AND SUPPORTIVE CARE FOR PSYCHOLOGICAL AND PSYCHO-SOCIAL COMPONENTS OF CANCER PAIN

Management of pain may require use of psychological and physical therapies. Relaxation, imagery, biofeedback, hypnosis, transcutaneous electrical nerve stimulation and other therapies have been applied in management of cancer pain [102, 103, 118, 119, 121, 123, 129, 162, 194, 195]. However, few controlled studies of these techniques have been conducted in cancer patients. The use of hypnosis has been utilised in cancer patients with some reports of success [195, 196]. The objective is to lead to reduction in the pain experience, increase control by the patient, increase activity and improve quality of life.

SUMMARY AND CONCLUSIONS

The management of oral and maxillofacial cancer pain is a major problem facing the health care professions. The majority of patients with cancer require some type of pain management during the course of their disease. The significance of pain in the head and neck region can be magnified because of the importance of the region in growth and development, and psychological and social interactions.

Management strategies for oral and maxillofacial cancer pain are based upon principles of management of acute and chronic pain. Knowledge of the medical and dental conditions as well as the effects of the cancer treatment are necessary to understand the multiple causes of pain and to select therapy. Pain may occur in patients with head and neck and oral cancers, and malignant diseases treated with aggressive systemic chemotherapy. In order to better understand pain in the oral cavity and the head and neck in cancer patients more controlled studies on incidence, severity, location, aetiology and management is needed.

Inappropriate or inadequate management of pain may result from a number of factors that include a limited number of controlled studies, the lack of education of health professionals, and a lack of multidisciplinary and collaborative approaches in pain management. Furthermore, concerns of overuse of medications in general may result in inappropriate use of analgesics. Lack of use of adjunctive medications and techniques is almost universally reported. The application of physical and psychological techniques of pain control require study in patients with cancer of the head and neck.

Further research on pain in head and neck cancer may result in several benefits. Prediction of pain during and after treatment will allow for preventative strategies to be employed or more timely intervention. Patients who are at greater risk of cancer pain could be identified, and therapies directed at pain control could be evaluated. Studies of preventive and therapeutic interventions are needed.

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