

Chapter 13

Persistent Pain in Breast Cancer

Although breast cancer is basically non painful, and that is why it is malignant, pain usually arise from its complications, whether due to spread of the disease to painful sites, or due to its therapy. Advances in the researches in the field of pain, gave the possibility to understand management of chronic pain and to do measures to prevent the occurrence of some preventable forms, but by any means, a good control of pain must be our target in patient management.

In breast cancer, persistent pain as a symptom occurs approximately in half of patients. Not all patients' present difficulty in their management and only about 9% of them has pain of difficult therapeutic or diagnostic problems.

In the mean time, the stress associated with the disease may lead to psychological disturbances, which will share in the exaggeration and initiation of pain problems. The fear of disfigurement, therapeutic failure, and uncontrolled pain will drive some of patients into anger, anxiety and depression, creating a vicious circle that has to be broken to get a good control of the painful condition.

The affinity of this type of cancer to disseminate will need a good and thorough patient assessment to get grasp of the presented clinical stage and to make a good plan for patient management. Moreover, one has to understand how therapeutic measures can inevitably produce a painful syndrome, such as post-mastectomy pain, post-irradiation neuralgia, and some forms of aseptic bone necrosis from corticosteroid therapy. Some other forms of pain may be produced by a non-malignant associated condition as disc lesions or diabetic neuropathy, or back pain from prolonged phases of bed rest and inactivity.

Breast Cancer Pain

Three broad categories of pain mechanisms may be posited: ongoing nociceptive, neuropathic processes, and psychological influences.

Nociceptive Pain

This term is applied when pain is perceived to be corresponding with tissue damage associated with an identifiable somatic or visceral lesion. This type includes:

- A. Somatic pain that originates from somatic structures and is typically well localized, sharp, aching throbbing or pressure like.
- B. Visceral pain that originates from viscera and is often diffuse, gnawing, cramping, aching, sharp or throbbing.

Neuropathic Pain

It is believed to be sustained by a site of aberrant somatosensory processing in the peripheral or central nervous system, most strongly suggested when there is a sensory affection in the form of hypoesthesia, dysesthesia, or allodynia, sometimes with loss of sensation and burning form of pain.

Pathogenesis of Pain Syndromes

Syndrome	Causes	Percentage
1. Postmastectomy pain	Surgical differentiation	19%
2. Intercostal Neuralgia	Herpes Zoster Rib metastasis	7% 5%
3. Heavy painful arm	Irradiation fibrosis Axillary recurrence	19% 7%
4. Low back pain	L1 metastasis L4. 5 sacroiliac metastasis	5% 7%
5. Joint pain	Hip, femur Shoulder & humerus	7% 5%
6. Upper abdominal pain	Liver metastasis	12%
7. Neuralgias	Sciatic & ulnar neuralgia	7%

Acute Pain Syndromes

Acute pain in breast cancer is usually related to patient's management, and can be prevented. Acute pain hospital service should be available to prevent the occurrence of these forms. Pain is usually simple, cause-related, and has a short duration. Acute pain syndromes associated with breast cancer are:

- Pain associated with diagnostic interventions e.g. Myelography, Percutaneous biopsy.
- Postoperative pain.
- Pain associated with chemotherapy infusion techniques as intravenous infusion pain due to venous spasm, chemical phlebitis or extravasation.
- Pain associated with chemotherapy toxicity e.g. mucositis, corticosteroid induced perineal discomfort.

- Pain associated with hormonal therapy as hormone-induced pain flare in breast cancer.
- Pain associated with immunotherapy e.g. interferon-induced acute pain. Pain associated with radiotherapy e.g. early onset brachial plexopathy, subacute radiation myelopathy, incident pains associated with positioning and mucositis.
- Pain associated with infection due to altered immunity e.g. acute herpetic neuralgia.
- Pain associated with analgesic techniques e.g. injection pain, opioid headache, spinal opioid hyperalgesia syndrome, epidural injection pain.

Breast Cancer related chronic pain syndromes

A. Tumor Related Pain Syndromes

1. Bone pain

Metastatic tumor in breast cancer can be presented by a variety of bone pain symptoms. It is a form of ongoing nociceptive pain, increases significantly with mobility, and is relieved in the majority of patients by rest and with the use of steroidal or non steroidal anti-inflammatory drugs, but in some patients more invasive techniques are mandatory to control such pain as vertebroplasty or bone fixation. Syndromes related to bone metastasis are:

I. Generalized or multifocal-metastases and marrow expansion

II. Vertebral syndromes

- C7-T1 syndrome: pain referred to the interscapular region.
- T12-L1 syndrome: pain referred to the ipsilateral iliac crest or the sacroiliac joint.
- Sacral syndrome: radiates to buttocks, perineum and posterior aspect of the thigh.
- Atlantoaxial destruction and odontoid fractures: radiates over the posterior aspect of the skull to the vertex and exacerbates by flexion of the neck.

III. Back pain: should be viewed as potential indicator of epidural compression.

IV. Pain syndromes of the bony pelvis and hip: cause pain with ambulation.

2. Headache and facial pain

- Intracerebral tumor metastasis with manifestation of increased intracranial tension and will respond to dehydrating measures (steroids, diuretics and positioning) in addition to analgesics.
- Leptomeningeal metastases.
- Skull base metastases.

- Painful cranial neuralgia as trigeminal and glossopharyngeal neuralgia.

3. Tumor involvement of the peripheral nervous system.

- Radiculopathy.
- Cervical plexopathy.
- Brachial plexopathy “early onset transient”.
- Post herpetic neuralgia.

4. Pain syndromes of the viscera

E.g., liver metastases cause hepatic distention syndrome.

B. Cancer Therapy Related Chronic Pain Syndromes

1. Post chemotherapy pain syndromes

As chronic painful peripheral neuropathy, and avascular necrosis of femoral or humeral head.

2. Chronic post surgical pain syndromes e.g.

- Post mastectomy pain syndrome
It affects 20% of women who undergo breast surgery, although it has been reported to occur after almost any surgical procedures on the breast but it is most common after procedures involving axillary dissection. Pain may begin immediately or as late as many months following surgery. The onset of pain later than 18 months following surgery is unusual and a careful evaluation to exclude recurrent chest wall disease is recommended. It is usually constricting or burning in character that is localized to the medial arm, axilla and anterior chest wall. On examination, there is often an area of sensory loss within the region of the pain and sometimes trigger points can be palpated in the axilla or chest wall. The patient may restrict movement of the arm, leading to frozen shoulder as a secondary complication. Its etiology is believed to be related to damage of the intercostobrachial nerve, a cutaneous sensory branch of T1, 2, 3. There is marked anatomic variation in the size and distribution of the intercostobrachial nerve and this may account for some of the variability in the distribution of pain observed in patients with this condition.
- Phantom breast after mastectomy
Occurs in 15% of patients and appears to be related to the presence of preoperative pain, it tends to start in the region of the nipple and then spread to the entire breast. The character of the pain is variable and may be lancinating, continuous or intermittent.

- Heavy painful arm
Edema of the upper limb after radical mastectomy is very common due to radical axillary evacuation of lymph nodes. Intermittent lymphangitis usually occurs due to lymph stasis, especially in diabetic patients with inflammatory signs and symptoms.

3. Chronic postradiation pain syndromes

Radiation-induced brachial plexopathy: “Progressive plexopathy of a delayed onset which can occur 6 months to 20 years after a course of radiotherapy that included the plexus in the radiation portal.

In the pain clinic, National Cancer Institute Cairo University, the pain syndromes associated with breast cancer was found to have the following distribution:

Management of Breast Cancer Pain

We have to take into consideration the meaning of pain to the patient. It usually carries the mind of patient to failure of treatment, which in approximately 50% of patients; it is due to treatment success, as in post-mastectomy pain, irradiation fibrosis, herpes zoster, sciatic and ulnar neuralgia. They usually appear 6 months after treatment, which logically means in the patient’s opinion failure of treatment. Detailed explanation to the patients about the condition will dramatically affect their sufferings.

A second important point to be considered is that the presence of pain for a prolonged period will affect the function of the nervous system in a way that the threshold of pain will be lowered. Intolerable pain will be converted tolerable when supporting the exhausted or deranged perceptive system in such patients. This is the aim of medical treatment, rather with prescribing analgesics, which has a good controlling effect in all cases, and by itself can control 47% of cases.

I. Medical treatment

Prophylaxis

Preventing pain before operative interference, or what is called pre-emptive analgesia, is now regarded important. The tissue injury usually sets up a vascular, immunological, and sympathetic stimulation that will bring about a long list of inflammatory mediators in the form of peptides. The primary effect of these mediators is to stimulate the immune mechanisms and tissue repair. The effect of these mediators on nociceptors may cause stimulation of abnormal severe pain, which is difficult to control, and is manifested with hyperalgesia. It was found that preventing these effects on the sensory nerve is essential in preventing the

occurrence of post-surgical chronic pain syndromes. This can be done by using opioids, α_2 agonists, GABA agonists, or local anesthetic infiltration to the site before inducing surgical trauma.

- Trial to preserve the intercostobrachial nerve as possible during surgery.
- Slow rate of infusion of chemotherapy
- Avoidance of extravasation of chemotherapy infusion.
- Early rehabilitation and physiotherapy and encouragement of active movements to avoid frozen shoulder
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Pain Control

Two main tools are available (non-invasive drug therapy and minimally invasive procedures aiming for pain control) and can be used separately or in combination to control such pain. Pharmacotherapy in the form of analgesics constitutes the most common form of pain control in breast, and other cancer pain. It does not need equipment and experience compared to invasive methods used for pain relief. The most common disadvantages, which one should work to minimize during drug treatments, are tolerance and side effects. These should be regarded with the start of treatment and not to permit its development. It needs also continuous monitoring to make the control of pain and side effects reasonably good. The advantages of drug therapy comprise its simplicity and availability for large number of population to be treated in the same time. However, interventional pain therapy in the form of minimally invasive procedures aiming for pain relief can play an important role in controlling pain in certain situations e.g. percutaneous neurodestructive procedures, neuroaxial drug delivery devices and vertebroplasty.

A. Pharmacotherapy (analgesics)

We have to stick to the following rules during drug treatment otherwise, we will get easily side effects or failure of drug treatment. The rules are:

1. Analgesics are prescribed by the clock

Do not permit the pain to appear to give the analgesic, as bouts of pain and pain relief will accelerate the development of tolerance. Drugs are given in the sufficient or full clinical dose and repeated according to their duration of action in order to keep the plasma level in a fairly constant level. So, the prescription of when required is now condemned.

2. Analgesics are given by a satisfactory route

The oral drugs constitute a good route, which is always satisfactory to the patient. However, it is not suitable for unconscious patients or patients with persistent nausea and vomiting. Oral drugs usually pass through a phase of liver metabolism before reaching their target, a fact which lowers drug availability and increases the effect of metabolites which should be counted in chronic drug administration. Transdermal route especially patches with long-term effects lasting for 72 hours is an ideal option for patients with persistent nausea and vomiting. The rectal route and Intramuscular route are always inferior as drug absorption is irregular. Intravenous route, by continuous infusion or by patient controlled analgesia PCA is the ideal, and usually needed to determine the effective daily dose in some cases. Subcutaneous route is also effective, and is regarded in some situations as good as the intravenous route. Also the transmucosal, nasal or sublingual routes are good options.

3. Analgesics are prescribed by a ladder

There is an agreement about the scheme of treatment by analgesics to go through a three ladder steps, and one should not jump any step in the ladder system.

- Step I: A non steroidal anti-inflammatory drug NSAID is usually used, together with an adjuvant. We have to remember that the NSAIDs have a ceiling analgesic action and we must not exceed the clinical doses to get analgesia, as this will only result in production of side effects. The appearance of new selective COX II inhibitor drugs minimizes very much the incidence of occurrence and severity of side effects.
- Step II: A weak opioid as codeine, dextropropoxyphene, oxycontin, tramadol; to be added to strengthen step 1.
- Step III: You may replace the weak opioid with a strong opioid as morphine, oxymorphone, and fentanyl patches. The NSAIDs can potentiate opioid analgesia and reduce opioid consumption.

4. Always try to give adjuvants

Adjuvants are non analgesics, which have an analgesic effect in certain conditions as neuropathic pain. They were claimed also to potentiate morphine analgesia. The analgesic outcome is greatly enhanced by the use of adjuvants.

B. Adjuvant drugs

(i) Classical Adjuvants

These are drugs given to relief anxiety, to promote sleep and delay central exhaustion. This group includes:

1. The serotonergic antidepressants

A representative of this group is “Amitriptylene” or Tryptizol. Its action is to raise the central 5HT (Serotonin), which is important neurotransmitter acting with opioids in the analgesic body system.

It is important to recover the pain threshold, and to guard against tolerance to the administered opiates. It is important to remember that only serotonergic antidepressants are needed. The dose needed here is very small, ranging from 10 to 30 mg. daily.

2. The anticonvulsants

The representatives are “Carbamazepine” or Tegretol. They are essential if there is any element of neuralgic pain. Tegretol 200 mg tablets, initially twice daily are usually the starting dose, and it is gradually increased up to 2 tablets three times daily. It has a leucopenia effect, which necessitates periodical blood cell analysis. Other members are clonazepam and phenytoin and the new gabapentin.

3. Corticosteroids

They constitute one of the chemotherapeutic agents. They are particularly useful in cases of bone, brain, or liver metastatic pain. Their dramatic effect on pain necessitates their use in a loading dose, which can be adjusted afterwards.

4. Anxiolytic drug

Benzodiazepines are a favorable group of adjuvants to abolish anxiety and promote good sleep.

(ii) Non-Classical Adjuvants

This group includes;

1. Osmotic laxative

Lactulose may be needed to prevent constipation associated with opioid therapy. One has to note that the constipating effect is not related to the strength of the opioid, as constipation by dextropropoxyphene is more than that of morphine.

2. Anti-emetics

Are needed when there is nausea and/or vomiting. Dopamine antagonists are readily available and very suitable to use with opioids. It is useful to note that opioids can produce nausea only in ambulatory patients, and it is very responsive to treatment. Serotonin antagonists as ondansetron are used for persistent cases.

3. Antibiotics**li. Interventional pain therapy**

It is the use of minimally invasive procedures to control pain. Percutaneous neurodestructive procedures, implanting different devices for neuroaxial opioid delivery and vertebroplasty are the most common pain relief procedures used to control cancer pain. This type of therapy can offer excellent quality of pain relief

for long duration without much impact on these patients especially when properly performed for selected patients, as most of these procedures can be performed percutaneously, under local anesthesia with radiological guidance and requires minimal hospital stay mostly for a couple of hours or days. So, in terminal cancer patients (life expectancy less than one year) it is recommended to interrupt or destroy the pain-transmitting pathway at a suitable target. This destruction should be attempted as early as possible to get benefit from the quality of pain relief with the possible reduction of analgesic medications and hence their side effects and burden on different organ functions which may be already impaired by cancer or its therapy.

As a rule, this line of pain therapy is indicated only in localized cancer pain except for hypophsectomy in case of generalized bony metastases or insertion of implantable systems for neuro-axial opioid delivery. Percutaneous vertebroplasty can be performed to alleviate pain originating from vertebral fractures due to tumors or their metastases. Bleeding tendency and local infection at the site of intervention are general contraindications, beside other contraindications specific for certain procedures and will be mentioned later within each procedure. The following are some examples of these interventions:

1. Percutaneous Cervical Cordotomy

It is destruction of the lateral spinothalamic tract to interrupt pain transmission from the contralateral side of the body below the level of the lesion. It is performed percutaneously under local anesthesia and CT-guidance. At the level of C1-C2 as lesioning at that level is almost guaranteed to produce analgesia below C4 or C5 as pain fibers enter the cord through the dorsal horn and then may ascend several levels before crossing over and taking their final position in the spinothalamic tract at the anterolateral quadrant at the spinal cord.

It is indicated in patients with unilateral cancer pain of somatic origin below the level of the shoulder. The success rate is more than 90% with excellent quality of pain relief, which lasts for more than one year and is associated with loss of pinprick sensation and temperature discrimination.

The major risk of percutaneous cordotomy is respiratory decompensation and this risk increases with pre-existing severe pulmonary disease and bilateral lesions producing high levels of cervical analgesia, as the automatic respiratory fibers course through the reticulospinal tract, which is so adjacent or may mingle with fibers of the spinothalamic tract. Ipsilateral ataxia and motor weakness may occur in few cases but fortunately in a temporary manner.

2. Posterior Rhizotomy (Sensory Nerve Root Destruction)

Localized somatic cancer pain especially at the chest or trunk e.g. rib metastases can be alleviated by percutaneous posterior root destruction using subarachnoid neurolytic agents. 80-85% success rate can be obtained following the procedure. It may be followed by motor affection if anterior (motor) nerve roots are unintentionally destroyed. It is contraindicated in case of intraspinal tumor extension at the target level.

3. Celiac Plexus Destruction

85% success rate in alleviating upper abdominal visceral cancer pain originating from liver metastases. Celiac plexus is a prevertebral sympathetic plexus situated in the retroperitoneal space at the level of the first lumbar vertebra. It can be performed percutaneously, under L.A. and by the aid of biplanar fluoroscopy, using a total volume of 50 ml of 50% alcohol as a neurolytic agent injected bilaterally. Postural hypotension and diarrhea may follow this procedure but fortunately in a transient manner and respond well to symptomatic treatment. Therefore, in severely dehydrated patients, it is relatively contraindicated and preoperative adequate hydration is essential.

4. Paravertebral Sympathectomies

To alleviate sympathetic maintained pain in the upper extremities, especially following surgery or radiotherapy. Satellite or upper thoracic sympathectomy can be done percutaneously with 70-80% success rate by the aid of biplanar fluoroscopy or under CT guidance. Complications in the form of unintentional destruction of the nearby nerves and the occurrence of pneumothorax may rarely occur.

Hypophysectomy

Pituitary destruction is indicated in generalized bony cancer pain not responding to pharmacotherapy e.g. metastatic breast cancer. It can be performed transnasally with good success rate but with some risk of mortality and morbidity (CSF leak, diabetes insipidus....). Hypothalamic pain suppressing response activated by elimination of hormonal feedback of the pituitary gland is the most accepted theory for the mechanism of action of such procedure.

Local infiltration or intercostal block in a rib metastasis, an epidural block in cases of vertebral metastasis with localized pains, and interpleural block which is particularly useful in pleural involvement, all can be applied using a mixture of local anesthetic and steroids. This proved successful in relieving such pain for one to four weeks and can be repeated.

Implantable Systems for CNS Drug Delivery Systems

The appearance of severe intolerable opioid side effects or tolerance in a patient who was opioid sensitive at the start of this treatment is a good indication to test for the effect of neuroaxial opioid before permanent implantation. Opioids are the main drugs used either alone or mixed with other medications (e.g. local anesthetics). Lesser dose, better analgesic response and fewer side effects are the main advantages of neuroaxial opioids, and implantation of these systems offer better stability and less infection.

Percutaneous vertebroplasty (PVP)

It is a minimally invasive therapeutic procedure that involves injection, under-radioscopic guide, of an acrylic polymer (mostly methyl methacrylate) into a vertebral body with pathologic compression in an effort to relieve pain and provide stability. As, it can achieve an immediate stabilization and pain resolution in 70-90% of the cases. It can be performed under local anesthesia ± sedation with a short hospital stay for one night or even as an outpatient procedure. Vertebroplasty may be performed in combination with radiation therapy or in conjunction with decompressive surgery.