Chapter 7
Acupuncture and Moxibustion for Side Effects of Chemotherapy in Cancer Patients

Jillian L. Capodice, Mitchell C. Benson and Dawn L. Hershman

Abstract This chapter introduces the major classes of chemotherapeutic drugs, including the alkylating agents, antimetabolites, vinca alkaloids, taxanes, antibiotics, hormone analogs and targeted drugs. The mechanisms of a number of chemotherapy-induced side effects such as nausea and emesis, cancer-related pain, peripheral neuropathy and vasomotor symptoms (e.g. hot flashes) are outlined. A detailed literature review expounds some of the major studies that have tested acupuncture and moxibustion as potential treatments for chemotherapy-induced side effects, including the use of acupuncture and moxibustion for chemotherapy-induced nausea and vomiting, peripheral neuropathy in patients receiving platinum and taxane-based regimens, vasomotor symptoms (hot flashes) in breast cancer patients receiving adjuvant hormonal therapy and prostate cancer patients receiving androgen deprivation therapy.

7.1 Introduction

Conventional treatment of cancer includes surgery, radiation, chemotherapy, immunotherapy and an array of other therapies such as bone marrow transplantation and gene therapy. Chemotherapy is the administration of drugs aimed at destroying cancer cells in order to have a beneficial effect on the history of the illness. Chemotherapy aims to arrest tumor progression and the ultimate goal of chemotherapy is a cure, defined as long-term, disease-free survival (Longo et al. 2012).

The landscape and practice of medical oncology has changed in the past 20 years as curative treatments have been discovered for several malignancies including testicular cancer and some leukemias and lymphomas (Brunton et al. 2011). Neo-adjuvant, adjuvant chemotherapy and hormonal treatments have been shown to increase disease-free survival and reduce recurrence in many cancers such as breast, colorectal and lung cancers. Molecular targeted drugs and immunotherapy are the newest medicines in the armamentarium of cancer chemotherapy treatments.

J. L. Capodice (✉) · M. C. Benson · D. L. Hershman
Department of Medicine, Columbia University, 10th Floor,
161 Fort Washington Avenue, New York, NY 10032, USA
e-mail: jc2346@columbia.edu

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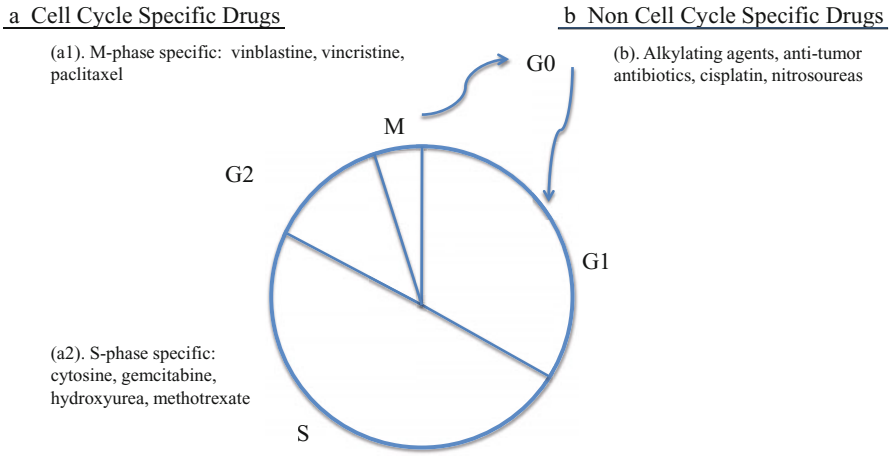

Fig. 7.1 The various phases of the cell cycle. The fundamental cell cycle events of DNA replication and cell division occur during interphase and mitosis, respectively. Interphase is the longer phase and includes the subphases G1, S and G2. G0 corresponds to cells that are withdrawn from the cycle into a resting state (G0). Cell cycle specific drugs include those that affect the cell during the M (a1) or S (a2) phase. Noncell cycle specific drugs (b) may act at any point in the cell cycle

A basic understanding of chemotherapy requires familiarity with the cell cycle as most chemotherapeutic drugs strive to cause cytotoxicity to the cancer cell either at specific or non-specific phases of the cycle. Drugs targets are often metabolic sites crucial to cell replication and the fraction of cancer cells in the replicative cycle is what makes them susceptible to chemotherapy. All dividing cells consist of three subpopulations: non-dividing cells that are terminally differentiated, proliferating cells, and resting cells that may be recruited into the cell cycle. In tumor cells, all three populations exist (Kufe 2010).

The cell cycle is composed of four phases during which the cell prepares for mitosis. Cells committed to divide enter the G1 phase, cellular processes prepare the cell for deoxyribonucelic acid (DNA) synthesis, the S phase, a second resting phase, G2, and subsequent mitosis, the M phase. The M phase is where the chromosomes condense and the cell separates into two daughter cells. Figure 7.1 depicts the cell cycle and the specificity of some cytotoxic agents. Cellular checkpoints also require a multiplicity of players and signaling events such as proteins, cyclin-dependent kinases and ion-signaling events and molecules that are crucial for cell replication. Many of the molecular-targeted drugs that have been designed are due to our increased knowledge of these players and targets.

Tumor kinetics and the effect of various chemotherapeutic drugs must also be understood. The growth rates of cancer cells are due to proportions between the number of actively dividing cells, the doubling time of the cell cycle and the rate of cell loss. Therefore, variations in these proportions are factors responsible for both the rate of tumor growth and the effect that a chemotherapeutic agent may have on a tumor. Cell cycle phase specific drugs have a plateau with respect to tumor

cell killing ability whereas non cell cycle specific drugs have a linear dose-response curve. The concept of achieving cell kill in a logarithmic fashion is the fundamental of chemotherapeutic dosing concepts (Brunton et al. 2011).

The current major classes of anticancer drugs include the alkylating agents, antimetabolite analogs, vinca alkaloids, taxanes, antibiotics, hormones and hormone antagonists and other agents such as enzymes and molecular-targeted drugs. Table 7.1 lists the major chemotherapy drug classes' mode of action and frequent indications.

7.2 Anticancer Drugs

7.2.1 Alkylating Agents

The mechanism of action of alkylating agents is to impair cell function by binding to nucleophilic groups that interfere with the integrity and function of DNA inducing cell death (Brunton et al. 2011). The most important alkylation sites are DNA, RNA and proteins. Alkylating agents are non cell cycle specific but are dependent on cellular proliferation and are most toxic to rapidly dividing cells. Alkylating agents are used to treat a variety of solid and hematologic cancers. Acute toxicities of alkylating agents are largely due to their delayed effect on tissues with low mitotic indices including the liver, kidney and mature lymphocytes. The most common toxicities include bone marrow depression (dose limiting), neurotoxicity, other organ toxicity (e.g. pulmonary fibrosis, hepatotoxicity and gonadal dysfunction), nausea and vomiting, stomatitis and alopecia. The alkylating agents are further subdivided into classes according to their structure and mechanisms and include the nitrogen mustards, nitrosoureas and platinum coordination complexes (Kufe 2010).

Nitrogen mustards are non cell cycle specific alkylating agents. Their main mechanism of action is to break down and covalently modify DNA bases. Overall, the nitrogen mustards are strong local vesicants and require quick administration. They are most frequently used in treatment of hematologic malignancies. Cyclophosphamide is commonly used in combination to treat acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and Hodgkin's and non-Hodgkin's lymphomas (Longo et al. 2012). The nitrogen mustard ifosfamide is used in combination treatment for testicular cancer (Siegert et al. 1994).

The nitrosoureas are known for their lipid solubility and instability. Their lipophilic nature enables them to rapidly penetrate the blood-brain barrier thus they are commonly used to treat a variety of brain tumors. Nitrosoureas may also cause delayed and bone marrow depression and kidney damage. Carmustine is used as an intravenous administration to treat brain tumors and as an implant (polifeprosan 20 with carmustine implant) in the adjuvant treatment of high-grade and recurrent malignant glioma and glioblastoma multiforme (Brem et al. 1995).

The platinum coordination complexes have broad anticancer activity and are used in the treatment of many solid tumors including head and neck, esophageal, lung,

Table 7.1 Classification of major chemotherapeutic drugs

Drug (class)	Mode of action and frequent indications
Nitrogen mustards (alkylating agent)	Kill cells by attacking DNA Used to treat acute chronic leukemias, Hodgkin's disease, lymphomas, and certain cancers of the lung, breast, prostate, ovary and testis Cyclophosphamide is a common nitrogen mustard that acts by cross-linking DNA
Nitrosoureas (alkylating agent)	Subgroup of alkylating agents that act to inhibit changes necessary for DNA repair Cross the blood-brain barrier and are commonly used to treat brain cancers Carmustine and lomustine are the major drugs in this group
Platinum coordination complexes (alkylating agent)	Normally used to treat many solid tumors including lung, ovarian, colon, testicular, bladder, esophageal, breast and head and neck cancers Cisplatin, carboplatin and oxaliplatin are the major platinum agents
Folic acid, pyrimidine and purine analogs (anti-metabolites)	Block cell growth by interfering with certain activities, usually DNA synthesis Broken down in to folic acid, purine and pyrimidine analogs Used to treat acute and chronic leukemias, choriocarcinoma, and some tumors of the gastrointestinal tract, breast, and ovary Methotrexate is the most common folic acid analog that acts to inhibit dihydrofolate reductase 6-mercaptopurine and 5-fluorouracil are the most commonly used purine and pyrimidine analogs respectively
Anticancer antibiotics (natural products)	Diverse group of compounds that generally act by binding with DNA and preventing RNA synthesis Widely used to treat a variety of solid and hematologic malignancies Doxorubicin, dactinomycin, mitomycin and bleomycin are the most frequently used drugs in this category
Vinca alkaloids (natural products)	Act by blocking cell division during mitosis Commonly used to treat acute lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphomas, neuroblastomas, Wilms' tumor, and cancers of the lung, breast and testis Vincristine, vinblastine and vinorelbine are the main agents in this group All bind tubulin and prevent microtubule assembly causing arrest in metaphase
Taxanes (natural products)	Act by blocking cell division during mitosis *via* prevention of microtubule depolymerization Commonly used to treat breast, ovarian, lung, head and neck, bladder and prostate cancers Paclitaxel and docetaxel are the two major taxanes
Hormonal agents	Includes corticosteroids, estrogens, anti-estrogens, and anti-androgens that modify the growth of certain hormone-dependent cancers such as breast and prostate Tamoxifen for breast cancer and leuprolide for prostate cancer are common examples
Molecular targeted drugs	Act by altering molecular pathways and/or cell signaling molecules Imatinib is a common tyrosine kinase inhibitor Rituximab is a common monoclonal antibody that binds CD20 antigen on B-lymphocytes Trastuzumab binds the HER2 receptor

bladder, colon and ovarian cancers. Their general mechanism of action is to covalently bind to nucleophilic sites on DNA causing DNA cross-links that inhibit synthesis of DNA, RNA and proteins. The most commonly used platinum complexes are carboplatin, cisplatin and oxaliplatin. Clinical toxicities include bone marrow depression, renal damage, ototoxicity, nausea and vomiting and peripheral neuropathy. Specifically, carboplatin is generally better tolerated and it has been noted that while it may not be as effective as cisplatin in the treatment of testicular, head and neck and esophageal cancers, it may be an effective alternative for patients that have cisplatin toxicities (Go and Adjei 1999; Brunton et al. 2011). Oxaliplatin, widely used in the treatment of colorectal and gastric cancers causes dose limiting toxicities of bone marrow depression and diarrhea as well as peripheral neuropathy often triggered by exposure to cold liquids in the mouth and throat and paresthesia in the upper and/or lower extremities (Goyle and Maraveyas 2005; Dolan and Fitch 2007; Sharma et al. 2007).

7.2.2 Anti-metabolites

Anti-metabolites are drugs that are analogs to naturally occurring metabolites of DNA and RNA synthesis. In the history of cancer treatment, the anti-metabolite folic acid analogs produced the earliest temporary remissions in leukemia and the first cure of a solid tumor (Farber and Diamond 1948; Berlin et al. 1963). Anti-metabolites interfere with the availability of normal purine or pyrimidine nucleotide precursors and act to inhibit or compete in DNA or RNA synthesis. They are cell cycle specific, exerting their maximal cytotoxic effects in the S phase of the cell cycle. The major classes of anti-metabolites include the folic acid, purine, pyrimidine and cytidine analogs.

Of the folic acid analogs, methotrexate is the most commonly used and its mechanism of action is as an inhibitor of dihydrofolate reductase that then inhibits folate-dependent enzymes of purine synthesis. Methotrexate is currently used in the management of ALL in children (Pui et al. 2004) and as a component in a number of combination chemotherapy regimens used to treat breast, bladder, ovarian, and head and neck cancers (Longo et al. 2012). Common methotrexate toxicities include bone marrow depression, dermatitis, nephrotoxicity, gonadal dysfunction and hepatic fibrosis and cirrhosis.

Purine and pyrimidine analogs are a diverse group of anti-metabolites that inhibit RNA and DNA function. The most common pyrimidine analogs are fluorouracil (5-FU), capecitabine, gemcitabine and floxuridine. 5-FU is commonly used as an adjuvant combination treatment with oxaliplatin or irinotecan and clinical toxicities include anorexia, nausea, stomatitis, diarrhea and bone marrow depression. The most common purine analogs are 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG) and both are used in the treatment of ALL, AML and chronic myleogenous leukemia (CML) (Kufe 2010).

7.2.3 Natural Products

The category of natural products in chemotherapy refers to a variety of chemotherapeutic compounds that have been isolated from natural substances including plants, bacteria and fungi. These include the vinca alkaloids, anti-tumor antibiotics, taxanes, epipodophyllotoxins and camptothecin analogs.

7.2.3.1 Vinca Alkaloids

Vinca alkaloids are chemotherapeutic agents isolated from the periwinkle plant, *Catharanthus roseus*, a species of myrtle. The main vinca alkaloids used today, vincristine, vinblastine and vinorelbine, are used to treat various leukemias, lymphomas, lung, breast, and testicular cancers. The mechanism of action vinca alkaloids is cell cycle specific as they block cells in mitosis and impair the formation of mitotic spindles. The key side effects of vinca alkaloids include bone marrow depression, nausea and vomiting, diarrhea and peripheral neuropathy.

Specifically, vinblastine is normally used in combination with cisplatin and bleomycin for the curative treatment of testicular cancer (Einhorn 1997) and as a component in the regimen for Hodgkin's disease (Batty et al. 2012). Vincristine is regularly used in combination with glucocorticoids in the treatment of childhood leukemias and pediatric sarcomas as it is thought to be better tolerated by children than adults. Vinorelbine is used in combination with cisplatin in the treatment of non-small cell lung cancer (NSCLC) and is in Phase III studies in an oral dose form for NSCLC (Krzakowski et al. 2008).

7.2.3.2 Taxanes

Taxanes are semi-synthetic chemotherapeutic agents derived from the Western yew tree. The major compounds in this group include paclitaxel, nab-paclitaxel, and docetaxel. Taxanes also cause mitotic inhibition and conversely to vinca alkaloids, promote microtubulin-formation-induced mitotic arrest. Taxanes are widely used to treat ovarian, breast, lung, gastrointestinal, head and neck and genitourinary cancers. The most common toxicities of taxanes include bone marrow depression, allergic hypersensitivity reaction, fluid retention, myalgia and sensory peripheral neuropathy (Brunton et al. 2011).

7.2.3.3 Anti-tumor Antibiotics

Anticancer antibiotics are grouped according to their structure and chemistry and include dactinomycin and the anthracyclines such as idarubicin, epirubicin, and doxorubicin. The anthracyclines are derived from the fungus *Streptomyces peuceutius* and the structures of anticancer antibiotics vary slightly in comparison to their

clinical activity. Idarubicin is primarily used in the treatment of acute leukemias and doxorubicin and epirubicin are more active in solid tumors. As a group, the primary mechanism of action is blocking DNA transcription or complexing with DNA topoisomerase II, an enzyme crucial for replication and repair. Clinical toxicities include bone marrow depression, stomatitis, alopecia, gastrointestinal (GI) disturbances and rashes (Brunton et al. 2011).

Specifically, bleomycin is used in combination to treat testicular, penile, cervical, head and neck cancers and Hodgkin's disease (Grimison et al. 2010; Meyer et al. 2012). Doxorubicin is used in combination treatment for ALL, AML, breast, ovarian and bladder cancers (Leone et al. 2011). Mitomycin is used for the treatment of gastric and bladder cancers (Shariat et al. 2010; Hamaguchi et al. 2011). Mitoxantrone is used to treat AML and prostate cancers (Ho et al. 1998; Sartor et al. 2011).

7.2.4 Hormones

A variety of cancers including breast, uterine and prostate, have been found to be hormone dependant and research into the understanding of the endocrine pathways implicated in the development of these cancers led to the identification and use of hormone analogs as chemotherapeutic treatments. The general mechanisms of hormonal agents in the treatment of cancer are to alter neuroendocrine signaling pathways, compete with receptors, or block genes that have been found to promote tumor growth and survival. The main categories of drugs in this class include glucocorticoids, anti-estrogens, aromatase inhibitors (AIs), anti-androgens, and gonadotropin-releasing hormone agonists and antagonists.

7.2.4.1 Glucocorticoids

The use of glucocorticoids in the treatment of neoplastic disease is based on their ability to induce anti-proliferative and/or apoptotic signals in sensitive cells as well as their ability to suppress mitosis in lymphocytes. They are normally used in the treatment of childhood and adult acute leukemias and lymphomas. For example, induction treatment of ALL in children includes administration of prednisone and vincristine (Eden et al. 2010).

7.2.4.2 Anti-estrogens and Aromatase Inhibitors

Anti-estrogens and AIs are primarily used as treatment for breast cancer following the discovery of the role of estrogen in the development of breast cancer and supporting evidence from epidemiologic studies and preclinical research that showed that estradiol promotes estrogen receptor (ER) positive breast cancer cell growth (Kufe 2010). The anti-estrogen treatments for hormone receptor positive breast cancer

include the selective estrogen-receptor modulators (SERMs), the selective estrogen-receptor down regulators (SERDs) and the AIs. The mechanism of action of a SERM is to bind the ER and exert therapeutic effect by competitively inhibiting estradiol. Tamoxifen is the most frequently used SERM and its side effect profile includes hot flashes, vaginal atrophy, alopecia and nausea and vomiting. SERDs are pure anti-estrogens and do not have any estrogen agonist activity. Fulvestrant is only agent currently approved by the United States Food and Drug Administration (FDA) in this class although a number of agents are being tested in current clinical trials. Fulvestrant is generally well tolerated and the most common side effects are nausea, pain, vasomotor symptoms and headache (Brunton et al. 2011).

AIs block the function of the aromatase enzyme responsible for converting androgens to estrogens. AIs are now used as adjuvant treatment for post-menopausal women with HR-positive breast cancer. AIs are classified into first-, second- and third-generations according to potency, specificity and mechanism of action. The most commonly used AIs include anastrozole, letrozole and exemestane. The side effects of AIs vary slightly compared to the SERMs with regard to lower incidence of vaginal bleeding and hot flashes but higher incidence of musculoskeletal disorders and myalgias (Bonneterre et al. 2001). Other side effects include osteoporosis, fatigue and peripheral edema.

7.2.4.3 Anti-androgens and Gonadotropin-releasing Hormone Agonists and Antagonists

Anti-androgens and gonadotropin-releasing hormone (GnRH) agonists and antagonists are primarily used in the treatment of advanced prostate cancer; the collective term is androgen-deprivation therapy (ADT). ADT can alleviate cancer-related symptoms, normalize serum prostate-specific antigen, reduce bone pain and prolong survival in men with advanced prostate cancer (Sharifi et al. 2005). The most common GnRH agonists are leuprolide, goserelin and triptorelin and these agents act on the hypothalamic-pituitary-gonadal axis *via* a negative feedback mechanism which triggers the secretion of luteinizing hormone (LH) which causes a testosterone surge for about 1 to 2 weeks followed by suppression of LH with chronic GnRH administration (Conn and Crowley 1991). In 2009, a new GnRH antagonist, degarelix was approved by the FDA for the treatment of advanced prostate cancer. GnRH antagonists do not cause a hormone flare following administration (Klotz et al. 2008). Non-steroidal anti-androgens include flutamide, bicalutamide and nilutamide and these agents are most frequently used in combination ADT. Side effects of ADT in men with prostate cancer include hot flashes, fatigue, gynecomastia, anemia, weight gain, osteoporosis and decreased insulin sensitivity.

7.2.5 Targeted Drugs

The field of chemotherapy has evolved due to our increased knowledge about the molecular basis of cancer and spawned a new category of targeted molecular drugs

such as tyrosine kinase inhibitors, monoclonal antibodies and cytokines. The fundamental mechanisms of these agents are based on targeting players in pertinent molecular cascades and/or mutation pathways that proliferate specific cancers and turn signals on or off to elicit tumor arrest.

Research on the use of targeted molecular agents and in particular, monoclonal antibodies, has largely increased over the past 30 years following seminal work by Kohler and Milstein (1975). The use of molecular-targeted drugs is now common for the management of certain cancers including some leukemias and lymphomas, breast, lung, colon and head and neck cancers (Harris 2004; Derby and Czuczman 2011). Some of the most common molecular-targeted drugs that have fundamentally impacted cancer treatment include rituximab, a chimeric monoclonal antibody against CD20 lymphocytes for non-Hodgkin's lymphoma; trastuzumab, a monoclonal antibody directed against the HER-2 membrane receptor for HER-2 receptor positive breast cancer; bevacizumab, a monoclonal antibody against vascular endothelial growth factor A for colon, non-small cell lung and breast cancers; and imatinib, a selective inhibitor of the BCR-ABL tyrosine kinase for the treatment CML and gastrointestinal stromal tumor (McLaughlin et al. 1998; Slamon et al. 2001; van Oosterom et al. 2001; Savage and Antman 2002; Talpaz et al. 2002).

7.3 Side Effects of Chemotherapy

One of the most important problems secondary to drug resistance, are the toxicities and side effects of chemotherapy. It is well known that any agent targeted to kill rapidly proliferating neoplastic cells will also affect normal cells. Cells undergoing rapid transformation such as buccal mucosal, hair, gastrointestinal mucosal cells and the hematopoietic system are most often affected and most toxicity is reversible. However toxicities affecting organs such as the lung, kidneys and heart must be monitored for toxicities to these organs can be irreversible if recognized too late.

The term supportive care refers to principles and care given to improve the quality of life of a patient. The National Cancer Institute defined supportive care as follows; "The goal of supportive care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment" (http://cancer.gov/). Conventional treatments for chemotherapeutic toxicities include antibiotics, anti-emetics, growth factors and blood transfusions. In addition supportive care interventions include complementary and alternative medicine practices and procedures such as acupuncture. Practices with level 1 evidence are frequently termed "integrative" by the National Center for Complementary and Alternative Medicine (NCCAM) division of the National Institutes of Health (NIH) (http://nccam.nih.gov/).

Complementary therapies including acupuncture and moxibustion have been recently studied as potentially valuable supportive care interventions and research has been done testing acupuncture and moxibustion for a number of side effects commonly experienced during chemotherapy including nausea and vomiting, pain,

neuropathy and vasomotor symptoms. Many of these symptoms are thought to be at least partially mediated by the central or peripheral nervous systems and though all of the mechanisms of action of acupuncture and moxibustion have not been elucidated, acupuncture has been proven to have a number of neuromodulatory effects as demonstrated by basic science and large multicenter clinical trials (NIH 1998).

The pathophysiology of each abovementioned chemotherapy-induced side effect will be detailed, followed by an in depth review of the supporting literature on acupuncture and moxibustion for the treatment of each named side effect.

7.4 Pathophysiology of Chemotherapy-induced Nausea and Emesis

Nausea and emesis (vomiting) refers to nausea, vomiting and retching. Nausea is defined as a "subjectively unpleasant sensation associated with flushing, tachycardia and an awareness of the urge to vomit" (American Society of Health-System Pharmacists (ASHP) 1999). Vomiting is defined as a contraction of the abdominal muscles, descent of the diaphragm and opening of the gastric cardia that result in an expulsion of the stomach contents from the mouth. Retching is defined as spasmodic contractions of the diaphragm, thoracic and abdominal wall muscles without expulsion of the gastric contents (ASHP 1999). All three may exist as a sequence or as individual events that are not predictive of one another. Nausea is the most difficult to define and characterize as it is largely subjective. While physiologic signs such as tachycardia and increased salivation may be concurrent during an episode of nausea, they are not universally present.

Vomiting and retching are easier to quantify as both produce physical signs such as contraction of the abdominal walls, shifting of the diaphragm, and expulsion of stomach contents. The purpose of vomiting is to expel noxious contents from the gastrointestinal tract and most often (but not always) vomiting is preceded by nausea. Three vomiting phases have been characterized, a prodromal, ejection and post-ejection phase (ASHP 1999). These phases are defined physiologically. The prodromal phase is the coordinated interplay between the vomiting center and the gastrointestinal tract in order to prepare it for emesis. During this phase, vagal afferents stimulate the proximal stomach and are also partly mediated by vasoactive intestinal polypeptide in the gut. Finally initiation of retrograde contraction moves the contents of the upper small intestine to the stomach and corrals any noxious contents to be ejected. It also directs any remaining contents of the lower small intestine into the stomach and commences the prodromal phase. The ejection phase refers to the actual expulsion of stomach contents *via* coordinated contraction of the muscular stomach, net compression of the stomach, and ejection of the stomach contents. Finally the post-ejection phase refers to the cessation of vomiting, cessation of nausea (if previously present) and generally, the person feeling better (Baker et al. 2005).

7.4.1 *Neural Components and Neurotransmitters Involved in Vomiting*

The aforementioned events are controlled by the vomiting center (VC), a collection of neurons in the medulla oblongata that was characterized by Borison and Wang (1953). Both the VC and the gut are associated with neurotransmitters such as serotonin, dopamine, histamine, acetylcholine and substance P that propagate signals to the VC and circulate in the brain. Serotonin and substance P are thought to be primary and dopamine, a secondary mediator of the nausea and vomiting response respectively (Faerber et al. 2007; Tipton et al. 2007). Enterochromaffin cells (EC) in the gut have also been demonstrated to respond to toxic substances and may release serotonin *via* the hepatic portal system to the chemoreceptor trigger zone (CTZ) that is located in the area postrema (AP) region in the bottom edge of the fourth ventricle. Finally, the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus nerve also act as relay stations to coordinate an emetic response (Miller and Leslie 1994; Leslie and James 2000; Hornby 2001; Chin et al. 2006). While these mechanisms have been proposed, the exact organization and propagation of signals to the CTZ are not fully characterized. Moreover the AP is a unique area that is situated between the fourth ventricle that remains unprotected by the blood-brain barrier but in communication with the cerebrospinal fluid (CSF). It is this characteristic that is thought to significantly contribute to chemotherapy-induced nausea and vomiting (CINV) due to its exposure and ability to circulate potentially emetic toxins to the brain (Miller and Leslie 1994; Hornby 2001). Neural influences that convey the sensation of nausea such as emotion, olfaction and visual signals are also difficult to characterize and higher cerebral control is thought to be an important factor regulating nausea. Differences in the efficacy of standard anti-emetic drugs for nausea such as serotonin (5-HT) *vs* neurokinin (NK_1) receptor antagonists (the latter superior for nausea), implies that multiple neurotransmitters and cerebral responses coordinate nausea. Activation of the limbic system, vestibular system, and the hypothalamic-pituitary axis are also areas where sensations of nausea may be experienced in the cortex; however these have yet to be defined and may vary depending on the particular stimuli eliciting nausea (Sanger et al. 2006).

The main stimuli inducing CINV is the absorption of cytotoxic chemotherapy in the gut and resulting local (chemoreceptors, gut afferents) and central (CTZ, VC, AP, neurotransmitters, higher cortical functions) effects. It has been proposed that the pathomechanism of CINV is initiated by the presence and absorption of chemotherapeutic drugs in the gut and gut signaling to vagal afferents and the brainstem *via* the NTS and AP. Locally, cytotoxic drugs stimulate luminal cells that likely activate EC of the gastric mucosal layer and neurotransmitters including serotonin, substance P and cholecystokinin (Racke et al. 1996). Another proposed mechanism of CINV is thought to be the role of cytotoxic drugs on the CSF and its effect on the CTZ, NTS, AP and higher brain function (Racke et al. 1996). Figure 7.2 details systems thought to be involved in the pathogenesis of CINV.

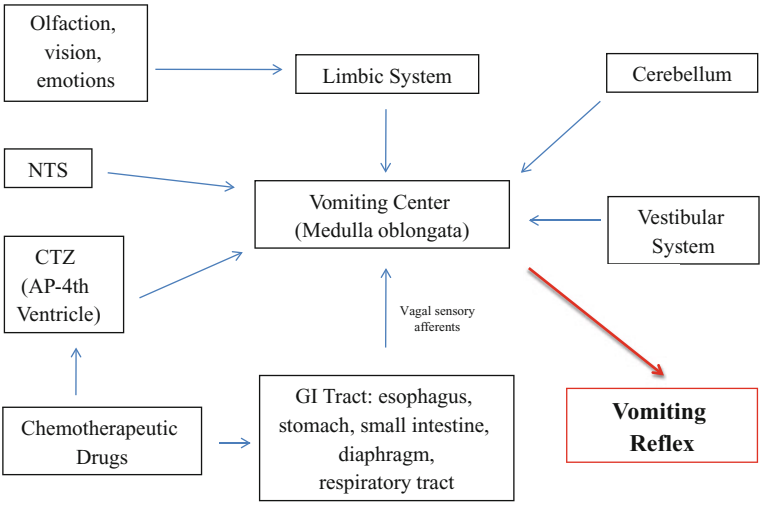

Fig. 7.2 The numerous systems thought to be involved in the pathogenesis of chemotherapy-induced nausea and vomiting. *AP* area postrema, *CTZ* chemoreceptor trigger zone, *GI* gastrointestinal, *NTS* nucleus tractus solitarius

7.4.2 Conventional Anti-emetics

The development of pharmaceutical anti-emetics has made a huge contribution to our knowledge and treatment of CINV. The use of modern anti-emetics can prevent vomiting in up to 70–80% of patients (Morrow et al. 2002). The four main anti-emetic drugs classes are: receptor antagonists, 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists, NK_1 receptor antagonists, and corticosteroids. Other drugs less frequently used and not discussed here include neuroleptics, benzodiazepines, cannabinoids, substituted benzamides, anti-histamines and botanicals such as ginger and mint.

7.4.2.1 Dopamine Receptor Antagonists

The dopamine receptor antagonists were the first main class of agents used for CINV. Most are either non-selective for dopamine $(D)_1$ and D_2 receptors are or D_2 receptor specific. D_2 receptor antagonists are thought to act by antagonizing D_2 receptors in the AP. However it is not known whether an increased circulation of dopamine is provoked by cytotoxic chemotherapy or if dopamine is released into the blood or AP. Finally, it is also know that cisplatin induced nausea and vomiting is non-responsive to D_2 receptor antagonist drugs (Ettinger et al. 2005).

7.4.2.2 5-HT_3 Receptor Antagonists

5-HT_3 receptor antagonists work by blocking 5-HT_3 receptors which may be activated and contribute to CINV due to potentially increased amounts of serotonin from

EC in the gut mucosa and systemically circulating 5-HT (Morrow et al. 2002). It is also thought that they are important in de-sensitizing the vagus nerve that may be prone to activation by other excitatory substances released from EC cells such as substance P. 5-HT_3 receptor antagonists seem to provide superior relief in the acute phase of emesis (0–24 h) and less relief for delayed vomiting (24–120 h) and nausea (Kufe 2010). 5-HT_3 receptor antagonists are commonly used in combination with NK_1 antagonists or corticosteroids. The 5-HT_3 receptor antagonists in use include granisetron, ondansetron, tropisetron, dolasetron and palonosetron. Reported side effects of 5-HT_3 drugs include headache, constipation, diarrhea and asthenia.

7.4.2.3 NK_1 Receptor Antagonists

Preclinical studies demonstrated the potential of NK_1 receptor antagonist drug administration for the treatment of CINV. NK_1 receptors act by blocking NK_1 receptors in the CTZ, NTS and gastrointestinal tract binding of substance P. In clinical studies the use of NK_1 receptor antagonists have demonstrated their superiority in treating delayed vomiting and as abovementioned, they are often used as combination treatment with 5-HT_3 drugs for acute and delayed CINV. Side effects of NK_1 receptor antagonists include headache, abdominal pain, dizziness, anorexia, hiccups and mild transaminase elevation (Campos et al. 2001; Cocquyt et al. 2001; Van Belle et al. 2002).

7.4.2.4 Corticosteroids

Dexamethasone was the first reported corticosteroid to be used as an anti-emetic for cisplatin induced nausea and vomiting and post-operative nausea and vomiting (Ettinger et al. 2005). Despite their widespread use and ability to raise the emetic threshold, the anti-emetic mechanism of action of corticosteroids is unknown. Possible explanations include anti-inflammatory modulation such as modulation of cortisol levels and eicosanoid metabolism, modification of the blood-cerebrospinal fluid barrier or inhibition of cortical input to the VC (Ettinger et al. 2005). In general, steroids are considered to be safe anti-emetics and common side effects include insomnia, indigestion and weight gain.

7.4.3 Acupuncture for CINV

Acupuncture is the insertion of fine, single-use, sterile needles into points in the body as determined by a system of acupuncture points and meridians. As a modality, it is often oriented in a traditional medicine framework as it is one of the most frequent procedures employed in the practice of traditional Chinese medicine (TCM). Acupuncture has become an accepted therapy for a variety of conditions including

CINV in adult and pediatric cancer patients (Shen et al. 2000; Ezzo et al. 2006; Reindl et al. 2006). Research on the potential mechanisms of action of acupuncture date back to the 1970s and one of the earliest proven mechanisms of acupuncture is the liberation of β-endorphin by acupuncture needling (Peets and Pomeranz 1978; Malizia et al. 1979). Numerous studies have since examined the other potential mechanisms of action of acupuncture and it has been demonstrated that acupuncture has an effect on endogenous opioids, various neurotransmitters, and cortical areas including the hypothalamus and amygdala (Gao et al. 1994; Hsieh et al. 2001; Chen et al. 2006). Other research has showed that acupuncture needling affects multiple ion channels and stimulates fibroblast, and local connective tissue responses (Langevin et al. 2007). Researchers are also analyzing acupuncture point-specific treatment effects and the morphology of acupuncture points and meridians (Ahn et al. 2008). There are also many studies on the various practices of acupuncture and how these may be correlated in a treatment effect (Langevin et al. 2011).

Acupuncture has been proven to treat a number of conditions including low back pain and CINV (NIH 1998). Studies on acupuncture for general nausea and vomiting and CINV often utilize the acupuncture point, Neiguan (PC6). PC6 is located on the anterior surface of the wrist between the tendons flexor carpi radialis and palmaris longus. It is measured by the proportional *cun* measurement system as three finger breaths from the wrist crease which corresponds as 2 *cun* (Chen 1999). Other commonly studied acupuncture points for nausea and emesis include Zusanli (ST36), Zhongwan (CV12), Weishu (UB21) and Hegu (LI4) (Lee and Fan 2009).

All of the large randomized controlled trials that have demonstrated the effectiveness of acupuncture in controlling nausea and vomiting have used the acupuncture point PC6 (Vickers 1996; Lee and Fan 2009). The largest systematic review of acupuncture for CINV scrutinized randomized trials of acupuncture point stimulation by any method (e.g. needling, electrical stimulation, magnets and acupressure) for the treatment of CINV (Ezzo et al. 2006). The authors included eleven trials ($n = 1{,}247$) in their assessment and demonstrated that acupuncture point stimulation reduced the incidence of acute vomiting (RR 0.82; 95% CI 0.69 to 0.99; $p = 0.04$). Acupuncture needle stimulation also reduced the portion of acute vomiting but not acute nausea compared to electroacupuncture and electroacupuncture reduced the proportion of acute vomiting more than manual acupuncture (RR 0.76; 95% CI 0.60 to 0.97; $p = 0.02$) (Ezzo et al. 2006).

The exact physiologic mechanism of action of acupuncture for CINV is still under investigation. The most recent studies suggest various mechanisms for the anti-nausea and anti-emetic effects of acupuncture including the ability of acupuncture to release neurotransmitters, the influence of acupuncture on peripheral nervous system (PNS) nerve transmission, and the effect of acupuncture on higher central nervous system (CNS) functions such as emotion and expectancy (Wayne et al. 2005; Streitberger et al. 2006; Enblom et al. 2011). Recent studies in animal models have looked at the effect of electroacupuncture on emesis in conscious dogs (Tatewaki et al 2005). These investigators demonstrated reduced episodes of vomiting following electroacupuncture at PC6 in vasopressin-induced emesis in dogs. This effect was reversible by naloxone suggesting the potential mechanism

of action of acupuncture needling is its effect on the endogenous opioid system. Other experiments proposed that the anti-emetic effect of acupuncture may be *via* decreasing transient lower esophageal sphincter relaxations (TLESRs). Zou et al. (2005) examined the effect of electroacupuncture on TLESRs in healthy human subjects. These investigators demonstrated that electroacupuncture at PC6 decreased the rate of TLESRs ($p < 0.02$) however this effect was not reversible by naloxone suggesting a non-opioid receptor mechanism. A third study looked electroacupuncture administration in cats and found that electroacupuncture at PC6 significantly reduced TLESRs *vs* sham stimulation ($p < 0.05$). This response was restored following infusion of a cholecystokinin-A receptor antagonist (CCK octapeptide) ($p < 0.05$) and naloxone ($p < 0.05$) but not phaclofen or tacrine (GABA antagonist and cholinesterase inhibitor respectively) (Wang et al. 2007).

Experimentation on the point specificity of PC6 utilizing functional magnetic resonance imaging (fMRI) has also been done. Yoo et al. (2004) demonstrated that acupuncture needling at PC6 resulted in activation of the left superior frontal gyrus, anterior cingulate gyrus and dorsomedial nucleus of the thalamus *vs* sham acupuncture. Bai et al. (2010) examined point specificity of acupuncture at PC6 *vs* an anti-emetic-irrelevant acupuncture point, Guangming (GB37) and found that there were distinct hemodynamic responses (as measured by fMRI) in subjects receiving stimulation at PC6 *vs* GB37. In particular, acupuncture stimulation at PC6 produced significant signal decreases in the amygdala, insula, perieacueductal gray (PAG) and the folcculonodular lobe of the cerebellum (nodulus and uvula) *vs* signal increases in the occipital cortex that occurred following GB37 needle stimulation. This study supports the distinct centrally mediated acupuncture point specificity of PC6.

7.4.4 Acupressure and CINV

Acupressure is based on meridian theory and is defined as the application of pressure to a specific meridian point by the use of the finger, hand, elbow, foot and/or acupressure band. A recent literature review of acupressure for CINV found a variety of studies, some that supported the use of acupressure for CINV and a few that showed no significant differences (Dibble et al. 2000; Melchart et al. 2006; Lee and Frazier 2011). Gardani et al. (2007) found that acupressure at PC6 controlled emetic symptomology in 68% of patients. There was no significant difference in efficacy related to tumor histotype but a trend showing decreased efficacy in patients receiving anthracyclines *vs* those receiving non-anthracycline containing combinations. Dibble et al. (2007) performed a multicenter, longitudinal randomized clinical trial of acupressure in women receiving chemotherapy for breast cancer. Their results demonstrated that there was a significant decline in the incidence of emesis for the PC6 acupressure group *vs* the placebo ($p = 0.002$) or usual care group ($p < 0.0001$) in delayed nausea (days 2–10). Overall, no prospective studies have analyzed differences between methodology and application of acupressure for CINV and more controlled studies are needed.

7.4.5 Moxibustion for CINV

Moxibustion is the use of heat to stimulate acupuncture points generated by preparations of the herb, *Artemisia vulgaris* (Chen 1999). Moxibustion has been widely used in many countries and is considered an important modality of traditional Chinese medicine (TCM) but there are fewer studies on moxibustion's mechanism of action and its role in treating CINV. Moxibustion (moxa) preparations include moxa-stick, -cone and -herbal cake applications. Moxa-stick moxibustion is performed by holding an ignited moxa stick a distance above the skin and warming the spot but not burning it. Herbal cake moxibustion is performed by placing an herbal cake on an acupuncture point(s), followed by the placement and ignition of moxa cones. Direct moxibustion is ignition of moxa cones or threads directly on the epidermis with or without the application of an emollient-type burn ointment. This type of moxibustion can cause scarring.

Research has suggested that moxibustion may have an anti-inflammatory mechanism of action and a recent study of moxibustion in mice demonstrated decreased levels of substance P, STAT6, NF-κB and iNOS in the nasal mucosa of mice that had received local moxibustion (Jung et al. 2012). Another study suggested that moxibustion may mediate mast cell morphology. These investigators administered moxibustion to a trinitro-benzene-sulfonic acid-induced rat model of colitis and demonstrated that the degranulation ratio of mast cells was higher in rats receiving moxibustion *vs* controls ($p < 0.05$) indicating a correlation between the effect of moxibustion on mast cells (Shi et al. 2011).

There are no basic scientific studies on the anti-emetic specific mechanisms of moxibustion however there have been a number of clinical trials. Lee and colleagues recently performed a systematic review of five clinical trials of moxibustion and CINV (Lee et al. 2010). The review assessed the trials based on outcomes including response rates, side effects, and quality of life. Of the four randomized controlled trials of moxibustion that fit the inclusion criteria, all failed to show any beneficial effect of moxibustion on tumor response rate. Of the two trials that assessed the frequency of CINV in patients treated with moxibustion, both studies reported significantly fewer episodes of nausea and emesis in subjects receiving moxibustion and meta-analysis showed significantly less nausea and vomiting in patients receiving moxibustion ($n = 80$; RR 0.38; 95% CI 0.22 to 0.65; $p = 0.0005$; heterogeneity $\chi^2 = 0.18$, $p = 0.67$, $I^2 = 0\%$) (Lee et al. 2010). The first of these two trials by Chen et al. tested moxibustion on the acupuncture point, Shenque (CV8) in subjects with nasopharyngeal cancer following radiation (Chen et al. 2000). The second study examined the effect of moxibustion treatment in subjects with advanced gastric cancers (Cao et al. 1997). Note, the full text of both of these articles is in the Chinese language so only the abstract was assessed. While there are a number of other studies on moxibustion in the literature, there is a paucity of research on moxibustion and it is clear that more studies are desperately needed.

7.5 Acupuncture for Chemotherapy-induced Pain and Neuropathy

Cancer pain is a significant problem in oncology and it is a debilitating side effect. Effective conventional treatments for cancer-related pain include pharmacotherapy and physical therapy. Acupuncture is becoming more widely used to treat chemotherapy-induced cancer pain and a number of well-designed studies have been recently published.

7.5.1 Acupuncture for AI-induced Arthralgia

Increase in breast cancer survival is largely due to the benefit of the hormonal therapies such as tamoxifen and AIs. Large clinical trials have demonstrated that AIs are associated with increased frequency of musculoskeletal disorders including myalgias and arthralgias and pain commonly affects joints including hands and knees. It has also been reported that the severity of arthralgias can cause up to 5% of patients to discontinue AI therapy. While the mechanism of AI-induced joint pain is still unclear, a variety of treatments including acupuncture are currently being tested in order to determine if they provide substantial and durable pain relief so that women can remain on these life saving drugs. Recent clinical trials by Mao et al. (2009) and Crew et al. (2010) have examined the effectiveness of acupuncture for the treatment of AI-induced arthralgia.

In the study by Crew et al. (2010), manual full body and auricular acupuncture *vs* sham acupuncture was administered to women with moderate to severe, self-reported musculoskeletal pain related to AI use for at least 3 months in duration. Outcome measures were the Brief Pain Inventory-Short Form (BPI-SF), Western Ontario and McMaster Universities Osteoarthritis Index and the Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands. Data was obtained at baseline (week 0), weeks 3 and 6 (endpoint). The results demonstrated that of 38 evaluable subjects, the difference in mean BPI-SF worst pain scores at 6 weeks was significantly lower in the true *vs* sham acupuncture group ($p < 0.001$). Differences between true and sham acupuncture with regard to pain related interference and pain severity ($p = 0.002$ and $p = 0.003$, respectively) were also reported.

Mao et al. (2009) similarly tested the subjects with the same inclusion criteria as Crew et al. (2010) but Mao's team utilized electroacupuncture. Of the 12 subjects enrolled and analyzed, reduction in pain severity as measured by the BPI-SF was found in women receiving electroacupuncture ($p < 0.001$). An additional secondary outcome, the Patient Global Impression of Change (PGIC) also demonstrated that there was a significant reduction in scores after 6 weeks of treatment with electroacupuncture.

Table 7.2 Chemotherapeutic drugs that may induce neuropathy

Drug (class)	Primary mechanism	Type and features of neuropathy
Bortezomib (targeted drug)	Unknown	Predominately distal sensory
Cisplatin, oxaliplatin (platinum coordination complex)	Damage to dorsal root ganglia, possible inhibition of axonal transport and DNA cross-linking	Predominately sensory neuropathy with sensory ataxia, sensory neuropathy induced by cold (oxaliplatin only)
Paclitaxel, docetaxel (taxanes)	Promotes microtubule assembly, possible damage to dorsal root ganglia and interference with axonal transport	Predominately sensory
Vincristine, vinblastine, vinorelbine (vinca alkaloids)	Interference with axonal microtubule assembly, impairs axonal transport	Sensorimotor and distal sensory

7.5.2 Acupuncture for Chemotherapy-induced Peripheral Neuropathy

Peripheral neuropathy (PN) is a common side effect of chemotherapy and its pathogenesis is poorly understood. PN most frequently occurs with administration of taxanes, platinum-based agents and vinca alkaloids (Table 7.2). PN can affect either sensory or motor axons and neuropathies are generally classified by which area of the cell body they affect as well as the main cause of the neuropathy. It is also known that risk of developing a toxic neuropathy is greater in patients with pre-existing neuropathy or in those taking other neurotoxic drugs. Chemotherapy-induced peripheral neuropathy (CIPN) is categorized as a toxic neuropathy that is associated with malignancy and is the direct effect of a toxic treatment. Other neuropathies associated with malignancies can be due to the cancer itself, as a consequence of a compromised immune system or as a paraneoplastic effect (Longo et al. 2012).

The neurotoxicity in CIPN (regardless of the agent that causes it) is a predominantly distal sensory neuropathy, characterized by pain, numbness, tingling and reduced functional capacity in the extremities (Henderson et al. 2003). Other symptoms can include paresthesias, ataxia, impaired vibration and joint position sense and loss of tendon reflexes. The severity and frequency of the neuropathy are related to the dose level, cumulative dose, dose-intensity, and infusion times, with more rapid infusions associated with higher incidences (Sparano et al. 2008). Neurotoxicity also appears to be more frequent when the agent is used in combination with other potentially neurotoxic agents and in patients with pre-existing neuropathy, e.g. diabetic or alcohol induced neuropathy (Henderson et al. 2003). CIPN can be dose limiting and may lead to dose reduction or cessation of therapy.

The pathogenesis of taxane-induced peripheral neuropathy is thought to be due to abnormal aggregation of microtubules in neuronal cells that cause neurosensory

symptoms. It has also been demonstrated that paclitaxel accumulates in the dorsal root ganglia leading to disturbances of cellular metabolism and axonal transport. The prevalence of peripheral neuropathy in patients treated with taxanes is about 30% (Theiss and Meller 2000; Quaasthoff and Hartung 2002) and symptoms have been reported to persist for up to 18 months after the cessation of taxane-based chemotherapy (Nakata and Yoriguji 1999).

The pathogenesis of cisplatin-induced neuropathy is due to its preferential uptake in the dorsal root ganglia that produces a dose-related sensory neuropathy (Cavaletti et al. 2004). Symptoms can include distal paresthesias and numbness, Lhermitte's sign and sensory ataxia. Cisplatin-induced sensory neuropathy most often occurs after a cumulative dose of at least 300 mg/m^2 but can occur with lower doses (Windebank et al. 1994; Albers et al. 2011).

Bortezomib-induced peripheral neuropathy (BIPN) is poorly understood and the incidence of peripheral neuropathy was reported in the Phase I studies of the drug (Aghajanian et al. 2002). The pathogenesis of BIPN is thought to be cumulative and dose related and prevalence has been reported to increase throughout the first five treatment cycles (Richardson et al. 2006). In a recent study by Richardson et al. (2006), 81% of patients reported BIPN and 71% experienced improvement after dose-modification or completion of therapy. Similar to the other chemotherapeutic agents, pre-existing neuropathy or concurrent use of other potentially neurotoxic drugs may increase the likelihood of onset of BIPN.

Recent reports suggest that nerve growth factor (NGF) may play a role in CIPN as mice treated with NGF, a putative neuroprotectant, demonstrated a reduction in the severity of oxaliplatin-induced neuropathy (Scuteri et al. 2010). Moreover, an inverse association between circulating levels of NGF and the severity of CIPN in cancer patients has been demonstrated (Lee and Swain 2006).

CIPN is difficult to prevent and treat. Symptomatic treatments include anti-depressants, anti-convulsants, non-narcotic and narcotic analgesics (Abuaisha et al. 1998). However, drug treatments are generally ineffective and limited by side effects. Acupuncture has been increasingly applied to the alleviation of pain, particularly among cancer patients and recently a few pilot studies have demonstrated that acupuncture may be beneficial in the treatment of this debilitating condition (Xu et al. 2010; Donald et al. 2011).

Donald et al. (2011) performed a retrospective evaluation of eighteen subjects that had be referred for acupuncture treatment with pre-existing PN after completing various chemotherapeutic regimens for hematologic and solid malignancies multiple myeloma (MM), ALL, CML, GI, breast and gynecological). The results demonstrated that 82% of patients (14 of 18) reported an improvement in symptoms following a course of 6-weeks of manual acupuncture. Patients were given individualized treatments however the most frequent acupuncture points used were Sanyinjiao (SP6), ST36, Taichong (LV3), LI4, Kunlun (UB60) and the Bafeng (EX-LE10) and Baxie (EX-UE9) points. Xu et al. (2010) performed a clinical trial of acupuncture treatment in 64 patients with paclitaxel or oxaliplatin induced peripheral neuropathy and found that acupuncture was superior to intramuscular injection of cobamamide ($p < 0.05$) though both were effective treatments. The acupuncture points utilized in this study included LI4, LV3, ST36, Qihai (CV6) and Quchi (LI11).

7.6 Acupuncture for Chemotherapy-induced Vasomotor Symptoms

7.6.1 Chemotherapy-induced Vasomotor Symptoms

The incidence of vasomotor symptoms due to hormonal treatment for breast or prostate cancer is common. In breast cancer patients, vasomotor symptoms are commonly reported in patients receiving adjuvant hormonal therapy with SERMs or AIs. The prevalence of vasomotor symptoms in women receiving SERMs has been reported to be as high as 80% (Jin et al. 2008) and up to 46% in women receiving AIs (Fallowfield et al. 2006). The pathomechanism of vasomotor symptoms (commonly called hot flashes or hot flushes) experienced by women receiving SERMs is due to the competitive inhibition of the drug (e.g. tamoxifen) to ER and blockage of the conversion of androgens to estrogens respectively. In women taking AIs, the suppression of peripheral aromatase leads to estrogen deprivation and both SERMs and AIs result in depletion of ERs and estradiol that are thought to be the main cause of the hot flashes. In men with prostate cancer, the pathomechanism of hot flashes is thought to be due to the decrease in circulating LH and follicle stimulating hormone (FSH) (Anderson 2003). The incidence of hot flashes in prostate cancer patients receiving ADT is close to 80% and it has been reported that hot flashes may persist up to 5 years after cessation of ADT (Higano 2003).

7.6.2 Acupuncture for the Treatment of Hormone Therapy-induced Hot Flashes

7.6.2.1 Breast Cancer

Only a few randomized controlled clinical trials of acupuncture for the treatment of hormone therapy induced hot flashes in breast cancer patients have been performed. Hervik and Mjåland (2009) initiated a prospective controlled clinical trial of 59 women receiving adjuvant therapy with tamoxifen and suffering from hot flashes and randomized them to true or sham acupuncture. A standardized acupuncture point protocol was administered and points included: LV3, Fengchi (GB20), Lieque (LU7), Taixi (KI3), SP6, Guanyuan (CV4), Daling (PC7) and Ququan (LV8). Over the 10-week period, the mean number of hot flashes was significantly reduced by almost 50% in the acupuncture group ($p < 0.001$) *vs* the sham group. A further 30% reduction was seen in the 12-week follow up period ($p < 0.017$). 22 of 30 patients experienced a reduction by at least 50% in the active treatment group, compared to 3 of 28 in the sham group ($p = 0.002$).

Nedstrand et al. (2005) randomized 38 patients with breast cancer and vasomotor symptoms to 12 weeks of electroacupuncture and 6 weeks of follow-up. The acupuncture points used in this study were Xinshu (UB15), Shenshu (UB23), Ciliao (UB32), Shenmen (HT7), SP6, LV3, PC6 and Baihui (GV20). In this study only five

women were actively using adjuvant hormonal therapy with tamoxifen throughout the study period and there was no difference in the mean number of hot flashes at baseline between the women receiving or not receiving tamoxifen treatment. However in women that were not receiving tamoxifen, a reduction in mean number of hot flashes was seen after 4 weeks of treatment *vs* 12 weeks in the women who were undergoing adjuvant hormonal therapy ($p < 0.05$).

Walker et al. (2010) recently performed a randomized controlled trial of acupuncture *vs* venlafaxine for the management of vasomotor symptoms in breast cancer patients receiving adjuvant hormonal therapy with either tamoxifen or AIs. 50 patients were randomly assigned to receive 12 weeks of acupuncture or venlafaxine and were followed up for 1 year post-treatment. All patients in the acupuncture arm were treated using a standardized protocol and a secondary protocol that allowed for selection of additional acupuncture points. The primary standardized acupuncture point protocol was UB23, KI3 and SP6. The secondary points that were used as needed according to the TCM diagnosis were Dazhui (GV14), GB20, Taiyuan (LU9), LV3, GV20, ST36, PC7 and HT7. The primary outcome, hot flash frequency, demonstrated a significant effect as both the acupuncture and venlafaxine groups experienced a decrease in hot flashes by about 50% and a return toward the baseline at follow up. This study also showed that there was a significant difference in adverse events (AE) in the venlafaxine group *vs* the acupuncture group ($p < 0.002$) as there were 18 incidences of AEs in the venlafaxine group and zero in the acupuncture group.

7.6.2.2 Prostate Cancer

There have been a few clinical trials of acupuncture for the treatment of ADT induced hot flashes in prostate cancer patients. Capodice et al. (2011) performed a pilot study of acupuncture in 16 men with prostate cancer experiencing hot flashes. The results demonstrated that at 7 weeks, patients reported a significant decrease in hot flashes ($p = 0.04$) with an average of 6.00 ± 2.40 (mean $\pm$ standard deviation) hot flashes per day as compared to 9.57 ± 3.98 at baseline. Decreasing frequency of hot flashes continued at the 14 week follow-up with patients reporting an average of 2.63 ± 1.20 hot flashes per day ($p = 0.001$). Decreased hot flash frequency was maintained over a follow up period of 14 weeks without acupuncture treatments, and at the 28-week follow-up, the frequency of hot flashes was slightly increased but still significantly decreased as compared to baseline 3.2 ± 1.7 ($p = 0.01$). The acupuncture points utilized in this study included full body standardized manual acupuncture and auricular acupuncture points including: SP6, UB15, UB23, Gaohuang (UB43), LV3, Zhaohai (KI6), LU7, HT7 (full body points) and auricular points including Shenmen, brain, kidney, liver and upper lung. Ashamalla et al. (2011) performed a pilot study in prostate cancer patients receiving ADT and found that acupuncture reduced the incidence of hot flashes from a mean of 28.3 hot flashes per day at baseline to 10.3 ($p = 0.0001$) at 2 weeks post-treatment, 7.5 ($p = 0.0001$) at 6 weeks and 7.0 ($p = 0.001$) at 8 months. The acupuncture point protocol administered in this study included Yanglingquan (GB34), SP6, KI3, ST36, UB15, UB23, Taiyang (EX-HN5), HT7, PC6 and LI11.

7.7 Safety Profile of Acupuncture and Moxibustion in Oncology

Standard safety practices, practice guidelines and ongoing research continue to support the safety of acupuncture in the oncologic setting. Safety studies in the literature demonstrate that acupuncture is safe. Only six cases of potentially serious adverse events (SAE) were reported in a study of 97,733 patients receiving acupuncture in Germany. SAEs included exacerbation of depression, hypertensive crisis, vasovagal reaction, asthma attack and pneumothorax. Minor AEs included local bleeding and needling pain, both occurring in less than 0.05% of patients (Melchart et al. 2004). Another retrospective study estimated SAEs from acupuncture to be 0.05 per 10,000 treatments, and 0.55 per 10,000 individual patients respectively (White 2004).

Many clinical trials of acupuncture now follow both the Consolidated Standards of Reporting Trials (CONSORT) and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines. The CONSORT guidelines were comprised in the mid-1990s and act as a basic checklist for reporting in a randomized controlled trial (Altman et al. 2001). The STRICTA guidelines have improved both the design and reporting of clinical trials of acupuncture as they suggest that methodology specific to acupuncture including needling details, rationale and control to be interventions are to be reported (MacPherson et al. 2010).

In the clinic, cancer patients require specific care and it is important that clinicians are familiar with potential co-morbid conditions and toxicities. A guideline for the treatment of cancer patients with integrative therapies has been established by the Society for Integrative Oncology. The guidelines are based on grading recommendations according to the clinical encounter and intervention. Grade 1A evidence exists for acupuncture as a complementary therapy when pain is poorly controlled, for CINV and for post-operative nausea and vomiting (Deng et al. 2009). Updating the guidelines to include contraindications such as lower level of normal limits for platelet count, absolute neutrophil count and other reasons based on the judgment of the clinical team are warranted (Capodice 2010; Lu and Rosenthal 2010).

Practical issues related to administering acupuncture in the oncology clinic should also be mandated and Clean Needle Technique (CNT) is required by most state licensing boards in the United States. CNT mandates hand washing, universal precaution, immediate isolation of needles and use of sterile, disposable, guide-tube needles. The FDA regulates acupuncture needles as medical devices mandating device material biocompatibility and sterility (21CFR880.5580). However acupuncture as a term, is considered heterogeneous. The strict definition is the administration of thin, filiform needles intended to pierce the skin in the practice of acupuncture however acupuncture may be used as a term to encompass other procedures such as intradermal needles, injection of substances into acupuncture points, laser therapy, other perturbations of points and sometimes even moxibustion.

For moxibustion, there is no guideline for the administration of safe practices apart from textbooks of Chinese Medicine (Chen 1999). Moxibustion has important and unique practices and potential adverse events associated with it. Reported adverse events of moxibustion include burns, itching, infection, allergy, respiratory tract sensitivity and xerophthalmia (Park et al. 2010).

Moxibustion, a modality that involves burning an herb over selected acupuncture points is an area where more research is needed in order to make treatment recommendations and safety guidelines.

7.8 Conclusion

The administration of chemotherapy is life saving treatment for adults and children with solid and/or hematologic malignancies. The most common side effects and toxicities of chemotherapy include alopecia, bone marrow depression, nausea and vomiting, pain and vasomotor symptoms. While many of these side effects are reversible, in some cases, symptoms can persist for a number of years following chemotherapy treatment and can be dependent on both the pathomechanism of the side effect and/or the physiologic state of the host. Acupuncture, an integrative therapy, has been widely studied for its potential to ameliorate chemotherapy-induced side effects and has been proven to have neuromodulatory effects. Many of these side effects are likely mediated and/or propagated through the central and peripheral nervous systems and thus are effectively treated with acupuncture. Acupuncture is safe when performed by qualified practitioners and it is important to have safe and effective supportive care treatments for persons with cancer enabling the curative goal of cancer treatment, long-term, disease free survival.

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