Supportive Cancer Care with Chinese Medicine

William C.S. Cho
Editor

Supportive Cancer Care with Chinese Medicine

Springer

Editor
Dr. William Chi-Shing Cho
Department Clinical Oncology
Queen Elizabeth Hospital
13/F Block R 30 Gascoigne Road
Kowloon
Hong Kong SAR
chocs@ha.org.hk

ISBN 978-90-481-3554-7 e-ISBN 978-90-481-3555-4
DOI 10.1007/978-90-481-3555-4
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2009942718

Preface

Cancer is a chronic disease. There are increasing cancer survivors after curative cancer treatment and this makes supportive cancer care an important area that more attention is needed. Chinese medicine has a long history of practice; it has aroused much interest from both Oriental and Western countries. A number of laboratory evidences and clinical trials demonstrated the effectiveness and efficacies of Chinese medicine for supportive cancer care. This book attempts to take a comprehensive approach to overview the different areas of Chinese medicine for supportive cancer care.

This book not only serves as an introduction to novices to the area and a useful reference for those already involved, but also serves as a stimulus to these and others to employ alternative approaches to current cancer care.

Hong Kong
December 2009

William C.S. Cho

Contents

Contributors

Ting Bao Marlene and Stewart Greenebaum Cancer Center; School of Medicine, Center for Integrative Medicine, University of Maryland, Baltimore, MD, USA, tingbao@gmail.com

Aditya Bardia School of Medicine, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA, adityabardia@gmail.com

Huijuan Cao Centre for Evidence Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China, huijuancao327@hotmail.com

Dennis HT Chang College of Health and Science, Centre for Complementary Medicine Research, Penrith South DC, NSW, Australia, D.Chang@uws.edu.au

Yi-Hung Chen Graduate Institute of Acupuncture Science, China Medical University, Taichung, Taiwan, yihungchen@mail.cmu.edu.tw

Kevin W. Chen Center for Integrative Medicine, University of Maryland School of Medicine, Baltimore, MD, USA, chenke@umdnj.edu

Yung-Chi Cheng Pharmacology Department, School of Medicine, Yale University, New Haven, CT, USA, yccheng@yale.edu

Delia Chiaramonte Center for Integrative Medicine, School of Medicine, University of Maryland, Baltimore, MD, USA, dc@insightmedicalconsultants.com

Peter Dorsher Mayo Clinic, Rochester, MN, USA, dorsher.peter@mayo.edu

Thomas Efferth German Cancer Research Centre (DKFZ), Pharmaceutical Biology (C015), Heidelberg, Germany, t.efferth@dkfz.de

Edzard Ernst Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK, eernst@pms.ac.uk

Lixing Lao School of Medicine, Center for Integrative Medicine, University of Maryland, Baltimore, MD, USA, llao@compmed.umm.edu

Myeong S. Lee Division of Standard Research, Korea Institute of Oriental Medicine, Daejeon, South Korea; Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK, drmslee@gmail.com mslee@kiom.re.kr

Xun Li Centre for Evidence Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China, tina000341@163.com

Henry LM Liang College of Health and Science, Centre for Complementary Medicine Research, University of Western Sydney, Penrith South DC, NSW, Australia, h.liang@uws.edu.au

Jaung-Geng Lin Graduate Institute of Chinese Medical Science, China Medical University, Taichung, Taiwan, jglin@mail.cmu.edu.tw.

Shwu-Huey Liu Phyto Ceutica Inc, New Haven, CT, USA, shliu@phytoceutica.com

Jianping Liu Centre for Evidence Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China, jpliutcm@yahoo.co.uk

Zengfu Peng Mayo Clinic, Rochester, MN, USA, peng.zengfu@gmail.com

Peter K Plinkert Department of Otorhinolaryngology, Head and Neck Surgery, University Heidelberg, Heidelberg, Germany, peter.plinkert@med.uni-heidelberg.de

Stephen M. Sagar Radiation Oncology, Juravinski Cancer Centre, Hamilton, ON, Canada, stephen.sagar@jcc.hhsc.ca

Muhammad W. Saif Pharmacology Department; Department of Medicine, School of Medicine, Yale Cancer Center, Yale University, New Haven, CT, USA, wasif.saif@yale.edu

Francis Seow-Choen Seow-Choen Colorectal Centre, 3 Mt Elizabeth Medical Centre, Singapore, seowchoen@gmail.com

Serkan Sertel Department of Otorhinolaryngology, Head and Neck Surgery, University Heidelberg; German Cancer Research Centre (DKFZ), Pharmaceutical Biology (C015), Heidelberg, Germany, s.sertel@gmx.net

Zhou Shu-feng Discipline of Chinese Medicine, School of Health Sciences, RMIT University, Bundoora, VIC, Australia, shufeng.zhou@rmit.edu.au

Torkel Snellingen Centre for International Health, University of Tromsø, Tromsø, Norway, torkel.snellingen@gmail.com

Kok-Yang Tan Department of Surgery, Colorectal Service, Alexandra Hospital, Singapore, kokyangtan@gmail.com

Raimond K. Wong Department of Medicine, Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada, raimond.wong@jcc.hhsc.ca

Xiaoxiu Wu Beijing Ton-Ren-Tang Science Arts (Singapore) Co. Pte. Ltd, Singapore, sarahwu@singnet.com.sg

Ruixin Zhang School of Medicine, Center for Integrative Medicine, University of Maryland, Baltimore, MD, USA, Rzhan001@umaryland.edu

Chapter 1
Supportive Cancer Care Using Chinese Medicine

Raimond Wong and Stephen M. Sagar

Abstract Complementary and alternative medicine (CAM) has been increasingly utilized by cancer patients in developed countries. Among the various forms of CAM, traditional Chinese medicine (TCM) is one of the few that has a well constructed theoretical framework and established treatment approaches for diseases including cancer. Recent research has revealed growing evidence suggesting that TCM is effective in the supportive care of cancer patients during and after major conventional cancer treatments (surgery, chemotherapy and radiotherapy). This effectiveness seems to mediate mainly through three approaches: (1) Improvement of tumour response and reduction of adverse treatment effects; (2) Immunity modulation and (3) Enhancement of symptom control. This chapter reviewed the concepts behind which TCM treatment approaches in supportive care of cancer patients are formulated and the published laboratory and clinical evidence supporting the usage of various TCM treatment strategies including herbal medicine, acupuncture, dietary modifications and qigong energy therapy.

1.1 Introduction

Up to 80% of cancer patients in the Western countries have utilized some forms of complementary and alternative medicine (CAM) to support their conventional cancer therapies (Ernst and Cassileth 1998; Boon et al. 1999). Among the various forms of CAM, traditional Chinese medicine (TCM) is one of the few that has a well constructed theoretical framework and established treatment approaches for diseases including cancer. In its country of origin, TCM has been used for thousands of years for treating cancers and continuous to be a well accepted form of treatment modality for effective cancer management, particularly when used in combination with other major conventional therapies such as surgery, radiotherapy and chemotherapy.

R. Wong (✉)
Juravinski Cancer Centre, Hamilton, ON, L8V 5C2, Canada
e-mail: raimond.wong@jcc.hhsc.ca

W.C.S. Cho (ed.), *Supportive Cancer Care with Chinese Medicine*,
DOI 10.1007/978-90-481-3555-4_1,

The acceptance of TCM as an effective supportive treatment for cancer in China is likely rooted from deep cultural influence, as well as recent emerging evidence from clinical and laboratory research supports the potential effectiveness of TCM in cancer therapies. This chapter aimed to review the concepts behind which TCM treatment approaches in supportive care of cancer patients are formulated and the published laboratory and clinical evidence supporting the usage of various TCM treatment strategies including herbal medicine, acupuncture, dietary modifications and energy exercise (qigong) energy therapy.

1.2 Cancer: Traditional Chinese Medicine and Conventional Perspective

Traditional Chinese medicine recognizes the human body functions as a body-mind system that are connected not only by physical anatomical structures but also by theoretical communication channels, collectively known as meridian network, in which vital energy (qi) and informational signals (blood) travel to adjust and coordinate bodily functions (Ikemi and Ikemi 1986). This complex dynamic body-mind system constantly seeks to achieve homeostasis, a balanced and harmonic state, the healthy state. The system is also autopoietic that it can recreate itself and evolve through adaptation to changing environments with which the human body interacts. External and internal pathological factors can disturb this system resulting in a transient or permanent imbalance unhealthy state. The presence of an imbalance system can be detected through observable patterns of signs and symptoms, syndrome patterns, presented by the person affected. Similar imbalance of the system presenting with similar syndrome patterns can be caused by very different disease processes. For example, a syndrome pattern with fatigue, shortness of breath and back discomfort can be presented in a patient with a primarily untreated lung cancer or a treated colon cancer on adjuvant cancer treatment. Traditional Chinese medicine practitioners learned the skill of identifying and differentiating different syndrome patterns. Once a syndrome pattern is identified, treatment with various approaches including, dietary adjustment, qigong, massage (tuina), acupuncture and herbal treatment, that have been recorded to be effective in TCM literature, can be utilized to correct the syndrome patterns and rebalance the body-mind system. However, the process of healing of the body-mind system is also dynamic that syndrome patterns can change over time and a number of different treatment approaches for various patterns may need to be used to achieve system balance.

In conventional Western medicine, cancer is considered a development in which the transformed cells acquire the ability to disregard the constraints of its environment and the body normal control mechanisms. The main conventional treatment strategies are aimed to remove or destroy these cancer cells with aggressive approaches such as radical surgery, radiotherapy and chemotherapy that inevitably lead to treatment complications (Macek 1984; Wong et al. 2001). In TCM, however,

cancer is a systemic disease from the start, and the terrain is considered to be as important as the tumour itself (Schipper et al. 1995). The development of cancer is interpreted as a result of disturbance of the balance in the body-mind system by external and/or internal pathological (emotional) factors (Macek 1984). This disturbance affects the normal flow of vital energy and informational signals through the system resulting in unchecked, prolonged stagnation of these elements that in turn, transform normal healthy tissues in the stagnated area to morbid tissues and eventually cancerous growth. Vital energy may be viewed as a model for intra- and inter-cellular information and potential energy transfer. This would correlate with the known abnormalities of signal transduction, cell contact and electrophysiology of cancer cells (Coffey 1998; Cuzick et al. 1998; Kang et al. 2000). It has also been shown that there is increased fluid content and a stagnant blood supply in malignant tumours (Baxter and Jain 1989; Sagar et al. 1993; Milosevic et al. 1998). The emphasis of internal or emotional pathological factors in TCM is intriguing. Experiments in rats show that chronic restraint stress promotes lymphocyte apoptosis through modulating *CD95* gene expression via a pathway that involves opioid receptors (Yin et al. 2000). In other words, stress can influence both the function and structure of the nervous system that, in turn, may modulate lymphocyte gene expression, thereby influencing immunity and resistance to cancer (Yin et al. 2000). It is interesting that there is correspondence with the TCM model of cancer predisposition being associated with rising qi or liver fire (representing anger), and the scientific evidence that repressed anger both suppresses the immune system and may increase the risk of breast cancer in the so-called Type C personality (Amkraut and Solomon 1972; Temoshok 1985; Temoshok and Dreher 1992). The presence of cancerous growth then further generates more disturbance in the body-mind system through additional blockage of energy and signal flow and the secretion of factors, referred as a form of toxin that critically damage healthy organ functions. This continuous system disturbance leads to diminishing healthy qi that, in conventional medicine, is related to the body nutritional, hormonal and immune status. Throughout this process, a variety of syndrome patterns can appear depending on the types of imbalance present.

It is believed that if one can strengthen and rebalance the body-mind network, the normal pattern will be restored and this will help to resolve the cancer. Traditional Chinese medicine treatments for cancer aim to assist the cancer patient to reacheive body-mind system balance and treatment approaches are individualized with constant adjustment according to the pathological patterns present and the constitutional status of the patients. Consequently, approaches include reduction of stagnation of qi and blood, information signals; elimination of toxin and enhancement of healthy qi are commonly utilized. Success of treatment is reflected with elimination of syndrome patterns; improvement in patient's symptoms and overall being. In combination with major conventional Western medicine cancer treatment strategies, these TCM approaches have been shown to support cancer patients through their treatment with improved symptoms control, enhanced cancer treatment response and improved survival.

1.3 Traditional Chinese Medicine and Surgery

Surgery is the commonest strategy in managing cancer. In early stage where cancers are confined to an anatomical location, most cancers, for example, breast, lung, prostate and colorectal cancers, can be effectively managed or even cured with radical surgery. However, surgical procedures usually involve analgesia and destruction of normal anatomical structures. From a TCM perspective, any major surgery weakens the body, the healthy qi, causing a reduction in the immune function and generating imbalance of the body-mind network. Thus it is important to maintain normal functioning of the body-mind network through surgery to allow the system imbalance to readjust and the healthy qi to recover.

1.3.1 Herbal

1.3.1.1 Preoperative Nutritional and General Status Improvement

A number of strategies have been advocated in TCM practice to prepare patients for their up-coming surgery. The use of TCM formulas such as Shiquan Dabao Decoction (Decoction of Ten Powerful Tonics), containing herbs: *Panax ginseng* (ginseng), *Angelica sinensis* (Chinese angelica root), *Paeonia lactiflora* (white peony root), *Atractylodes macrocephala* (bighead atractylodes rhizome), *Poria cocos* (tuckahoe), *Cinnamomum cassia* (cinnamom twig), *Astragalus membranaceus* (astragalus root), *Ligusticum chuanxiong* (chuanxiong rhizome), *Glycyrrhiza uarlensis* (licorice root) and *Rheum palumatum* (rhubarb), that traditionally used to improve the healthy qi of the body has been suggested in most TCM practice. There is however, no published clinical trial to examine its usage in preoperative settings in cancer patients. In an in vivo study, this formula has been shown to enhance T-cell immunity, through intestinal Peyer's patches stimulation, and this function correlates with the description of enhancing healthy qi and exert anti-tumour and anti-metastatic effects (Ohnishi et al. 1998; Dai et al. 2001). Moreover, surgery always causes some loss in blood and usage of TCM formulas, such as the Decoction of Ten Powerful Tonics, which also possesses hematopoietic effects, is also practiced preoperatively (Ohnishi et al. 1990).

Traditional Chinese medicine also recognizes the importance of the ability to absorb nutrition. Without this ability, even with the provision of rich nutritional food, normal bodily functions will not be sustainable and will result in a decline of the general status and poor disease prognosis. In patients with suboptimal nutritional status due to systemic effects of cancer where poor appetite is one of the main symptoms, TCM practice has engaged herbal treatments to improve patients' nutritional and overall performance status for enhancing their tolerance to invasive surgical procedures such as radical cancer surgery. Commonly used TCM formulas including the popular Buzhong Yiqi Decoction (Decoction for Reinforcing Middle-energizer and Replenishing Qi) containing *Codonopsis pilosula* (dangshen), tuckahoe, bighead atractylodes rhizome, Chinese angelica root, stir-fried *Setaria italica* (millet

sprout) and stir-fried *Hordeum vulgre* (malt), astragalus root, *Cimicifuga heracleifolia* (buybane rhizome), *Bupleurum chinense* (thorowax root), *Amomum villosum* (villous amomum fruit) and licorice root. The potential usefulness of this formula in preoperative intervention has not been evaluated clinically, but in a randomized controlled study of patients suffering from cancer related anorexia-cachexia, patients randomized to this formula showed greater improvement of body weight, increased food intake and better quality of life when compared to controlled group. Its effect is comparable to a third group randomized to medroxyprogesterone, a hormone that has been a standard conventional treatment for cancer-related anorexia. The formula however had not induced any side effects while medroxyprogesterone usage was associated with fluid retention, vaginal bleeding and hypertension resulting in cessation of therapy in a few patients (Cai 2003). This preoperative intervention approach is thus worth further research for its potential in improving patient's tolerance to surgery.

Cautions have been raised regarding the use of herbs in the perioperative period, particularly for the fear of adverse events caused by the interactions between herbs with anaesthesia and with blood coagulation mechanisms. For example, herbs including bighead atractylodes rhizome, *Salvia miltiorrhiza* (red sage root) and chuanxiong rhizome have been found to have anticoagulation effects, while herbs like Chinese angelica root, *Carthamus tinctorius* (safflower), *Curcuma longa* (common turmeric) and *Leonurus heterophyllus* (motherwort herb) affect thrombus formation. *Pueraria lobata* (pueraria root), *Cornus officinalis* (Asian cornelian cherry fruit), *Corydalis turtschaninovii* (corydalis tuber), *Ginkgo biloba* (ginkgo seed) and *Epimedium grandiflorum* (epimedium) inhibit platelets aggregation. Thus, it is generally recommended to stop herbal consumption for at least 2 weeks before the surgery (Zhu 1998; Ang-Lee et al. 2001).

1.3.2 Acupuncture and Other Approaches

1.3.2.1 Reduction of Acute Postoperative Nausea and Pain

Unlike herbal treatment, a variety of acupuncture and related techniques have been evaluated for its effectiveness in the perioperative period for reduction of postoperative nausea and pain.

Postoperative nausea and vomiting is common among cancer patients following anaesthesia and surgery. Acupuncture treatment at acupoint PC6 has been shown to increase the anti-emetic effect of drugs for peri-operative and chemotherapy-induced nausea and vomiting (Dundee et al. 1986, 1989). Innovative randomized single-blind controlled trials have since confirmed these results (Al-Sadi et al. 1997; Schlager et al. 1998; Lee and Done 1999) and led to the NIH (US) consensus statement that, "acupuncture is a proven effective treatment modality for nausea and vomiting" (NIH Consensus Development Panel on Acupuncture 1998). Stimulation of PC6 may be done more conveniently with a small transcutaneous nerve stimulation (TENS) device, such as the Reliefband, which is worn like a wrist watch. In

a recent Cochrane database systematic review of randomized trials examine stimulation of PC6 using invasive or non-invasive techniques was showed to be effective in preventing postoperative nausea and vomiting. Side effects of PC6 stimulation were minor and there was no significant difference between the effectiveness of PC6 stimulation compared to antiemetic drug treatments (Lee and Fan 2009).

1.3.2.2 Reduction of Analgesia Requirement

Acupuncture was first known to the conventional medicine world by its demonstrated analgesic property. Subsequent studies have suggested possible mechanisms through induced endorphin secretion and modification of thalamus and cortical activities in functional MRI studies (Lin and Chen 2008; Luo and Wang 2008). Intraoperative use of acupuncture and related techniques has been examined in a few randomized trials. In one trial, patients undergoing hip arthroplasty were randomized to auricular acupuncture and sham control. The treatment group was treated with indwelling needles to lung, shenman, forehead and hip points while the control group received needles to four non-acupuncture points on the helix. The results showed a reduction of 21% of fentanyl during surgery in the treatment group (Usichenko et al. 2006). Several other randomized studies also support the effect of auricular acupuncture on anaesthetic requirements (Greif et al. 2002; Taguchi et al. 2002). However, acupuncture on a few selected body acupuncture points was not shown to be effective in reducing anaesthetic requirement (Morioka et al. 2002).

1.3.2.3 Acute Postoperative Pain Control

Acute postoperative pain control after cancer surgery has been a common subject of recent acupuncture studies. In a controlled trial of breast cancer patients after breast cancer surgery and axillary lymph node resection, acupuncture was found to significant improve pain control and range of shoulder movement compared to a controlled group without acupuncture. The importance of individualized selected acupuncture points in the successful management of patients was emphasized (He et al. 1999).

Post thoracotomy pain is another pain condition that the analgesic effect of acupuncture has been examined in randomized controlled trials. In one trial, body acupuncture points including LI4, GB34, TE8 and GB36 on the same side of the thoractomy. These points were chosen for its recognized influence on the chest wall, upper body and pain control. Treatments were given with electrical stimulation on the first 7 postoperative days. A sham group using non-piercing needles was used as control. Analgesic usage on postoperative day 2 was found to be significantly lowered than controlled group and there was a trend of lower pain score in the treatment group from day 3 to 6 but it was not significant statistically (Wong et al. 2006). In another trial, a more invasive approach was used. Two groups of patients were treated with implanted intradermal needles or sham needles prior to thoracotomy. The needles were left for 4 weeks postoperatively. The study result was a negative

outcome but was criticized for not a common TCM acupuncture practice (Deng et al. 2008b).

Evaluation of acupuncture effect in acute postoperative pain control continuous to be hampered by problems of appropriate sham control, placebo effects and multiple confounding variables. With the increase in evidence from randomized trials demonstrating the effectiveness of acupuncture and related techniques in postoperative pain control, acupuncture will likely be continuously used and examined as a component of acute pain control strategies after cancer surgery (Sun et al. 2008). The types of acupuncture techniques to be utilized should be carefully chosen to balance the ease of delivery and expected effectiveness based on TCM principles and practice.

1.3.2.4 Improvement of Postoperative Urinary Dysfunction

Apart from pain control, other symptoms arising in the acute post operative period has also been treated with acupuncture techniques. Patients underwent pelvic surgery commonly experience temporary urinary dysfunction that may lengthen hospital stay. In a couple of reported studies, acupuncture treatments using electrical stimulation, on body acupuncture points including ST36, SP6, TE5, ST28 and ST29, have been shown to improve urinary flow rate, lower residual bladder volume and shorten post operative hospital stay compared to controls (Shi et al. 2008; Yi et al. 2008). Another report on patients with urinary retention after rectal cancer surgery, acupuncture using various body points aimed to strengthen the flow of qi through Bladder meridian and improve water flow, was shown to be effective in relieving urinary retention in over 90% of patients (Dong et al. 2003). However, all studies still involved small number of patients and had suboptimal study design.

1.4 Traditional Chinese Medicine and Radiotherapy

Radiotherapy is one of main conventional treatment modalities for cancer. Upward to 50% or more of cancer patients undergo radiotherapy through the course of their diseases. For radiotherapy to be effective, the availability of optimal oxygen level among the treated cells is important since cancer cells that survive in a low oxygen tension environment are found to be more resistant to radiotherapy and some types of chemotherapy (Brizel et al. 1997; Fyles et al. 1998). However, it has been shown that there is increased fluid content and a stagnant blood supply in malignant tumours (Sagar et al. 1993; Milosevic et al. 1998; Baxter and Jain 1989). The microcirculation within a tumour is also very abnormal in functions and in anatomical distribution, as a result, there are regions within the tumour where the blood flow is sluggish. The impaired blood circulation leads to areas of poor oxygenation in the tumour and can induce radio-resistance. In TCM, stagnation of blood and vital energy is classically considered to be associated with tumours and conceptually describes the similar phenomena observed in recent scientific research.

Radiotherapy treatment typically creates a sense of warmth, dryness and ultimate atrophy of the irradiated volume of tissue. This leads to TCM interpretation that therapeutic radiation is a form of external heat factor that can drive away stagnated cold blood seen in tumour and has the effect of drying up the fluid accumulated in tumour causing a regression in its size. However, these effects can also affect irradiated normal tissue resulting in complications that characterized by dryness and shrinkage similar to what is observed in fibrotic tissue. Thus therapeutic radiation is also viewed as a form of heat toxin that can consume body fluid and blood. If excessively delivered to a particular area of the body, can affect the person not only locally but also systemically presenting with general sense of warmth, dryness, red tongue, irritability, fatigue and ultimately a reduction in the healthy qi. These observations are supported by the recent finding of radiation-induced endothelial cells damage resulting in initial vessel dilatation, leakage with tissue edema and eventual vessel collapse and consequent ischemic necrosis of tissue (Girinsky 2000). Several studies also reported the suppressive effect of the body immune system by therapeutic local radiotherapy also support the concept that radiation heat toxin can gradually consume the healthy qi of the person treated (Thomas et al. 1971; Hoppe et al. 1977; Uh et al. 1994).

Traditional Chinese medicine treatment strategies in combination with radiotherapy thus focus on the reduction in stagnation of blood and vital energy accumulated in the tumour and in facilitating the elimination of accumulated heat toxin in the normal tissue.

1.4.1 Herbal

1.4.1.1 Enhancement of Radiotherapy Response

Destagnation or detoxification herbs are used to promote the movement of blood and vital energy that has accumulated in pathological tissue, such as malignant tumors. Interestingly, the use of anticoagulants, such as heparin and coumadin (warfarin), as an adjunctive treatment to chemotherapy, has been shown to prevent the development of blood-borne metastases in animal laboratory studies, and to improve the survival of cancer patients in clinical studies (Lebeau et al. 1994; Hejna et al. 1999).

Traditional Chinese medicinal herbs have been extensively investigated in the laboratory and are known to have multiple pharmacological effects (Wang et al. 1992; Tode et al. 1993; Lau et al. 1994; Boik 1996a, b; Shoemaker et al. 2005; Yance and Sagar 2006). Many of these herbs are also proving to be anti-angiogenic agents that may improve tumour blood flow and oxygenation status (Yance and Sagar 2006). There are plenty of examples of TCM herbs that have destagnation properties and process multiple anticancer therapeutic properties. Ginseng has anti-tumour activity, inhibits platelet aggregation, and inhibits chemotherapy-induced immunosuppression. Licorice root acid has anti-tumour activity, is anti-inflammatory through increasing serum cortisol, and also increases natural killer (NK) cell activity against cancer cells. Astragalus root is a powerful stimulator

of the immune system, has anti-tumour activity and inhibits platelet aggregation. Chinese angelica root stimulates the immune system, has anti-tumour activity, inhibits platelet aggregation, and inhibits vascular permeability. Bighead atractylodes rhizome has anti-tumour activity, and is an anti-thrombotic and fibrinolytic agent. Ginkgo seed has multiple effects including inhibition of platelet activation factor (PAF), stimulation of the immune system, fibrinolysis and anti-thrombosis, scavenging of free radicals, and dilation of blood vessels to increase perfusion. The effects on the haemostatic coagulation system are intriguing as more evidence emerges suggesting the existence of an interactive roles of the bone marrow, hemopoietic system, and angiogenesis in the progression of cancer (Yance and Sagar 2006).

The possible usefulness of destagnation herbs was demonstrated in a randomized controlled clinical trial evaluating the combined modality treatment of Chinese herbal destagnation formula and radiotherapy in patients with nasopharyngeal carcinoma (Xu et al. 1989). In this trial, 90 patients received combined herbal and radiotherapy compared to 98 patients who were randomized to receive radiotherapy alone. The ingredients of the herbal formula included astragalus root, *Paeonia veitchii* (red peony root), chuanxiong rhizome, Chinese angelica root, *Prunus persica* (peach seed), safflower, *Spatholobus suberectus* (suberect stem), pueraria root, *Citrus reticulata* (green tangerine orange peel) and dangshen. The combined treatment group showed a statistically significant increase in local tumour control and overall 5-year survival as compared with the group treated with radiotherapy alone. The rate of local recurrence in the intervention group was halved from 29% in those receiving radiotherapy alone, to 14% in the group receiving destagnation herbs as well. The 5-year disease free survival was increased from 37% in the control group to 53% in the group receiving destagnation herbs. It is postulated that this herbal destagnation formula may have improved tumour microcirculation and increased tumour blood flow leading to an improvement in the oxygen tension inside the tumour. The oxygen tension increases the radiosensitivity of the tumour. In other words, the destagnation formula has acted as a radiation sensitizer. Results from several other randomized controlled studies using similar TCM destagnation and blood invigorating herbs in combination with radiotherapy supported the effectiveness of this strategy (Li et al. 2002; Liu et al. 2002).

In animal experiments, ginkgo seed has also been shown to increase perfusion and radiosensitivity (Kleijnen and Knipschild 1992; Ha et al. 1996). Chinese herbs, such as red sage root, which inhibit tumour oedema caused by free radicals, may also increase tumour perfusion, oxygenation and response to radiotherapy (Sagar et al. 1995; Kuang et al. 1996). Other herbs may directly sensitize neoplastic cells to radiotherapy (Sun et al. 1994). Some herbs may protect normal tissues from radiotherapy. For example, ginseng and *Panax quinquefolium* (American ginseng) water extract (Rh2 ginsenoside) radioprotect through mechanisms involving antioxidative and immunomodulating properties (Lee et al. 2005a). The presence of a variety of chemicals in a single herb; the common usage of multiple herbs for therapy and the multiple pharmacological actions of a single herb may explain the observed

multiple benefits of herbal treatment, in terms of radiosensitization of tumour; improved treatment tolerance and reduction of treatment side effects. The subtle balance between anticancer effects and protection of normal tissue, is however still unknown.

1.4.1.2 Improvement of Symptoms in Radiation Enteritis

Apart from radiation sensitization for cancer treatment, TCM herbal treatments have also been reported to successfully treat radiation-induced side effects. Radiation-induced enteritis is a common side effect in patient received radiotherapy for abdominal or pelvic cancers presenting with symptoms of abdominal cramps, diarrhoea, feacal incontinence and tenesmus. When chronic, ischemic changes and adhesions of intestine can occur and can severely affect patients' quality of life. Treatment of radiation enteritis has been mainly for symptomatic relief with dietary adjustments and medications. A TCM formula, known in Kampo medicine practice in Japan, called Daikenchuto that consists of three herbs: dry *Zingiber officinale* (ginger), ginseng and *Zanthoxylum bungeanum* (peppertree pricklyash seed) traditionally used for treating abdominal pain and distension has been reported to be effective in alleviating this condition (Takeda et al. 2008). This report illustrated a practical approach in the choice of herbal formulas for treatment. The herbal formula should best be founded on traditional TCM reported experience. This should be further supported by evidence of its effectiveness in related conditions and the presence of possible underlying mechanisms by which the herbal ingredients may exert their effects.

Ginger has been shown to increase intestinal blood flow and enhance bowel motility. Ginseng possesses anti-inflammatory effects and may reduce radiation-induced bowel inflammation and peppertree pricklyash seed induces intestinal neural acetylcholine release promoting intestinal motility (Satoh et al. 2001; Murata et al. 2002; Hofseth and Wargovich 2007).

Traditional Chinese medicine enemas have also been reported to be helpful in managing radiation bowel injury. A solution prepared mainly with astragalus root, bighead atractylodes rhizome, dangshen and *Coptis chinensis* (coptis root) has been shown to induce symptom improvement in over 90% of patients (Ding et al. 2004). Possible mechanism may involve the suppression of nitric oxide production resulting in less inflammation of the bowel mucosa. Experiments using this herbal solution on irradiated rat bowel mucosa showed a significant increase in the number and height of bowel villi suggesting mucosal cells regeneration was promoted (Ding et al. 2003).

1.4.1.3 Prevention and Treatment of Radiation Pneumonitis

Despite the advance in radiotherapy techniques for locally advanced lung cancer, radiation pneumonitis remains the most serious and often dose-limiting complication. Traditional Chinese herbal treatment may be able to prevent or treat radiation

pneumonitis. A proprietary TCM herbal infusion preparation, Shenqi Fuzheng Injection, with dangshen and astragalus root as the main components was evaluated in a randomized study. Fifty-eight lung cancer patients were randomized to a control group treated with radiotherapy alone and a treatment group with herbal infusion given on day 3 after radiotherapy initiation to 1 week after radiotherapy completion. Radiation pneumonitis of grade 2 or greater, according to RTOG criteria, was significantly less than the control group. Plasma level of TNF-alpha and ratio of IL-10/TNF-alpha was also significantly lower in the treatment group compared to that of control suggesting the herbal injection may be able to down regulate cytokines and thus effective in preventing and treating radiation pneumonitis (Liu et al. 2007). In another randomized study in patients with established radiation pneumonitis, Shenqi Fuzheng Injection combining with antibiotics and hormone therapy has been shown to shorten pneumonitis and enhance immune function in patients compared to controls (Zheng et al. 2007). Similar effectiveness in treating radiation pneumonitis was also reported using a different an oral TCM preparation, Qingjin Runfei Decoction. This preparation was formulated, according to TCM herbal properties, to literally clear the lung dryness and smooth lung function (Zhang et al. 2007b).

1.4.1.4 Other Symptoms

Other radiation-induced symptoms that TCM herbal treatment has been shown to be effective include radiation-induced oral mucositis, visual pathway damage, dermatitis and symptom patterns developed during radiotherapy for nasopharyngeal cancer (Xu et al. 2003; Ma et al. 2007; Song et al. 2007; Wu et al. 2007). The successful results of these studies again emphasized the importance in choosing TCM herbal formulas based on observed herbal properties and the symptom pattern differentiation to be treated. However, studies involving proprietary herbal combinations reporting without the herbal ingredients listed continue to be a significant problem in scientifically evaluation and the acceptance of study results, and represent one of the road blocks in understanding and advancing the science of TCM herbal treatments.

1.4.2 Acupuncture and Other Related Techniques

Although acupuncture has been shown in studies to be a useful modality for a variety of symptoms in cancer patients, along with other interventions, clinical studies focused in acupuncture for radiation-induced symptoms are scarce (Thompson and Filshie 1998). The fewer reports may be due to the relatively under utilization of acupuncture by patients undergoing radiotherapy. A recent study showed that there was only 1.9% of surveyed cancer patients used acupuncture (Swarup et al. 2006). Direct radiotherapy induced symptoms that have been reported to benefit from acupuncture include xerostomia, post irradiation masseter muscle contracture and radiation proctitis. Among these reports, radiation-induced xerostomia has been the most studied.

1.4.2.1 Reduction of Symptoms in Radiation-induced Xerostomia

Radiation-induced xerostomia is one of the distressing late side effects seen in patients who received radiotherapy that involved the parotid glands. Patients with this condition suffer loss of taste and difficulty in speaking and swallowing. Recently, acupuncture treatment has been found to increase blood flow to the parotid glands and may stimulate tissue regeneration in parotid glands damaged by radiotherapy (Talal et al. 1992; Blom et al. 1992, 1993; Rydholm and Strang 1999). A randomized controlled trial of 38 patients with radiation xerostomia was reported from the Karolinska Institute (Sweden) (Blom et al. 1996). Subjects were randomized to either deep acupuncture treatment or superficial acupuncture treatment. The latter group was used as the control, despite previous evidence that superficial acupuncture treatment can have a certain degree of effectiveness and should not be used as a control in acupuncture treatment trials. In this study it was found that in both groups, there was more than a 20% increase in saliva flow rate in more than 50% of patients. In the deep acupuncture group, 68% of patients demonstrated an increase in salivary flow rate. Changes in the control group were smaller and appeared after a longer latency phase. Moreover, patients in the treatment group reported less dryness, less hoarseness and improved taste. In another study, 70 patients with xerostomia due to either Sjögren's syndrome or irradiation were treated with acupuncture (Blom and Lundeberg 2000). A statistically significant increase in unstimulated and stimulated salivary flow rates (SFR) was found in all patients immediately after acupuncture treatment, and up to 6 months follow-up. After a review at 3 years, those patients who chose to be treated with additional acupuncture demonstrated a consistently higher median SFR, compared to those not having additional acupuncture. Despite, some limitations in the study's design, both studies provide evidence suggesting acupuncture can be effective in treating radiation-induced xerostomia, with minimal side effects. In a prospective single cohort, visual analogue assessed study of acupuncture in palliative care patients with xerostomia, there was a highly significant alleviation of subjective xerostomia (Rydholm and Strang 1999). Other studies are confirming the clinical use of acupuncture for relief of radiation-induced xerostomia (Johnstone et al. 2001; Braga et al. 2008; Cho et al. 2008).

At the Juravinski Cancer Centre (Canada), a phase I and II study of acupuncture like (AL)-TENS in the treatment of radiation-induced xerostomia has been completed (Wong et al. 2003). Forty five patients were randomized into three treatment groups with AL-TENS stimulation using the Codetron to three different sets of acupuncture points (Group A: CV24, ST36, SP6, LI4; Group B: CV24, ST36, SP6, PC6; and Group C, CV24, ST5, ST6, SP6, PC6). The goal of this study was to determine the optimum pattern of stimulation (based on TCM theory) prior to designing a placebo-controlled study. AL-TENS treatment was administered twice a week for a total of 12 weeks. Unstimulated and stimulated salivary flow rates before, during and after treatment were measured, and a survey of the patients' quality of life was assessed during a follow up of 1 year. There was an improvement in xerostomia symptoms with a mean increase in the visual analogue score at 3 and 6 months after treatment completion. All patients demonstrated a significant increase in the mean basal and citric-acid primed saliva production. The results suggest that AL-TENS

treatment improves saliva production and related symptoms in patients suffering from radiation-induced xerostomia. Treatment effects are sustained at least 6 months after completion of treatment. Built on the results of this phase I/II study, a randomized phase III trials is currently underway by the Radiation Therapy Oncology Group, comparing AL-TENS with oral pilocarpine in established radiation-induced xerostomia patients. A recent fMRI study showed activation of the insula region of the brain, the location associated with gustatory function suggesting one of the possible mechanisms of acupuncture effectiveness in xerostomia is the stimulation of the central nervous system that may be followed by a cascade of physiological effects (Deng et al. 2008a).

1.4.2.2 Reduction of Radiation Proctitis Symptoms

Only one reported study examined the use of acupuncture in radiation proctitis. In this study varies acupuncture points were used to treat acute radiation proctitis in cervix cancer patients undergoing radiotherapy and reported 73% complete response rate (Zhang 1987). At the Juravinski Cancer Centre (Canada), acupuncture has been used for patients who suffered from tenesmus, pressure sensation and increased mucous secretion per rectum during preoperative combined chemradiotherapy for locally advanced rectal cancer. In 15 symptomatic rectal cancer patients treated using only the acupuncture point GV20 weekly during the third to fifth week of radiotherapy, all patients reported marked improvement of their symptoms after one or two treatments (unpublished data). GV20 is classically used to treat organs prolapsed and to limit leakage symptoms. It is commonly indicated in treating bleeding haemorrhoid.

1.5 Traditional Chinese Medicine and Chemotherapy and/or Biological Modifiers

Chemotherapy and biological modifiers have been one of the main treatment modalities for many types of cancers. Increasingly, multiagents are being used and are found to be more effective than single agent therapy. However, the severity of side effects almost always positively correlates with the number of agents used and is often dose limiting. Minimizing chemotherapy and biological modifier treatment side effects can improve dose tolerance and may translate to better treatment outcome and better patients' quality of life. Traditional Chinese medicine treatments have been shown to potentially improve not only treatment side effects but also act synergistically with chemotherapy and other agents against cancer cells.

1.5.1 Herbal

1.5.1.1 Synergistic Actions Against Cancer Cells

Many TCM herbs contain a variety of chemicals that may act synergistically to increase tumour cell death (apoptosis), inhibit tumour cell division, increase the

proportion of immune cells within the tumour, and increase blood flow through the tumour (Motoo and Sawabu 1994; Yano et al. 1994; So et al. 1997; Ikemoto et al. 2000; Liu et al. 2000). These observable changes were found to be associated with changes in the balance of cytokines and other communicating peptides released by immune cells, resulting in a reduction in the proliferation of tumour cells and an increase in tumour cell death, whilst minimizing many side effects for normal tissues. This synergy appears to be secondary to inducing apoptosis, anti-angiogenesis, antagonism of the viral genome, and induction of an immune response. In addition, some herbs can reverse multidrug resistance (Zhou and Liu 2005).

Extracts of multiple Chinese herbs traditionally used for anti-cancer therapy, such as *Anemarrhena asphodeloides* (wind-weed rhizome), *Artemisia argyi* (argyi wormwood leaf), *Commiphora molmol* (myrrh), *Potentilla indica* (mock strawberry), *Gleditsia sinensis* (Chinese honeylocust spine), *Ligustrum lucidum* (glossy privet fruit), rhubarb, *Rubia cordifolia* (India madder root), *Salvia chinensis* (Chinese sage), *Scutellaria barbata* (barbat skullcap), *Uncaria rhynchophylla* (uncaria stem with hooks), *Vaccaria segelalis* (cow-fat seed), demonstrate growth inhibitory activity against various cancer cell lines, but limited inhibitory activity against normal cell proliferation (Shoemaker et al. 2005). Coptis root induces cell growth arrest and apoptosis by up regulating interferon-beta and TNF-alpha in human breast cancer cells (Kang et al. 2005). Recent meta-analyses confirm the utility for Chinese herbs to both enhance the control of particular cancers (particularly viral-induced cancers such as hepatocellular carcinoma and nasopharyngeal carcinoma) and reduce side effects of chemotherapy (Shu et al. 2005; Taixiang et al. 2005; Meng et al. 2008; Cho and Chen 2009a, b). Laboratory studies suggest that some herbs increase the effectiveness of conventional chemotherapy. For example, red ginseng acidic polysaccharide (RGAP) increases the cytotoxicity of paclitaxel (Shin et al. 2004) and *Phellinus linteus* (sanghuang) enhances the cytotoxicity of doxorubicin (Collins et al. 2006). A meta-analysis of Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer indicates a promising therapeutic gain (McCulloch et al. 2006). Occasionally herbs alone are associated with tumour regression. In one report, a 51-year old lady with pathological proven squamous cell carcinoma of the lung attained complete regression with sole treatment using a combination of herbs "*Hedyotis diffusa* (spreading hedyotis herb), *Ophiopogon japonicus* (dwarf lilyturf tuber root), *Taraxacum mongolicum* (dandelion herb), *Panax notoginseng* (notoginseng), *Cremastra variabilis* (bulb of Chinese tulip), American ginseng, *Houttuynin cordata* (heartleaf houttuynia herb), *Fritillaria cirrhosa* (fritillary bulb), *Pinellia ternata* (pinellia tuber)" (Liang et al. 2004). This reported anecdote is unusual, but deserves further exploration. More clinical trials need to be done to further evaluate this promising role of herbs in potentially improving the therapeutic gain.

1.5.1.2 Reduction of Chemotherapy Side Effects

Cancer patients receiving chemotherapy develop common side effects including gastrointestinal upset with nausea, vomiting, oral mucositis and diarrhoea; myelosuppression with lowered blood counts resulting in anaemia, bleeding and increased

risk of infection; skin toxicities with hair loss and dermatitis; poor appetite with weight loss and general fatigue and poor quality of life. From TCM perspective, most chemotherapies are causing disturbance in the balance of the body-mind network, affecting mainly the vital energy of the spleen and kidney system resulting in syndrome patterns such as deficient spleen qi that manifests as diarrhoea; heart fire manifests as stomatitis; disturbed spleen and stomach qi with nausea and vomiting and physically as damage to the stomach and intestinal lining (Rosenberg 1997). With weakening of the whole body-mind network, a reduction in the healthy qi is resulted with suppression of the immune system and a deterioration of the general status of patients.

1.5.1.3 Prevention and Reduction of Myelosuppression

Traditional Chinese medicine associates the depressed immunity and susceptibility to infection and cancer progression with the weakening of the body healthy qi. Treatment approaches using herbs are focused on the qi strengthening potential either by the herbs alone or by the ability of the herbs to strengthen the spleen function to improve nutrients absorption and transformation and to strengthen the kidney function that facilitate the formation of blood elements. This may be viewed as correcting the basic imbalance of the body-mind communication network and is reflected by an enhancement in immunity. This is called reinforce the healthy qi (Fuzheng) treatment and is mediated by specific group of TCM herbs collectively called Fuzheng herbs. Examples of these herbs include ginseng, *Ganoderma lucidum* (lucid ganoderma), astragalus root, Chinese angelica root, *Cordyceps sinensis* (cordyceps) and *Lycium barbarum* (wolfberry fruit), have been shown to enhance the body's defence mechanisms. Clinical studies, including two randomized trials, have found that cell counts of NK cells and CD4 (Th) lymphocytes were increased with the use of Fuzheng herbs (Ning et al. 1988; Ling et al. 1989; Chen 1990; Yu et al. 1990; Hou et al. 1991; Rao et al. 1991; Li 1992; Yu et al. 1993; Cao et al. 1994; Cheng 1994; Horie et al. 1994; Lin et al. 1995). These immunocytes are known to attack cancer cells. Many of these herbs are associated with an increase in cytokines, such as interferon and interleukin (Kawakita et al. 1990; Jin et al. 1994; Feng et al. 1995). In a study of gastric cancer patients, increased survival was found in the combined treatment group (receiving both Fuzheng herbs and chemotherapy) as compared with the chemotherapy-alone group (Wang 1990).

Single herb, particularly medicinal mushrooms, such as lucid ganoderma, cordyceps and *Lentinus edodes* (Shiitake mushroom), rather than a formula, have been used clinically in cancer patients for its immune enhancement and anti-cancer properties. Data from controlled clinical trials suggest that medicinal mushrooms may be beneficial as adjunctive anticancer therapies (Lin 2005; Matsui et al. 2002). A randomized controlled trial in colorectal cancer patients receiving curative resection compared adjuvant chemotherapy alone to chemotherapy plus an extract (PSK) from the fungus *Coriolus versicolor* (multicolored polypore). Both disease-free and overall survival was significantly higher in the group that received PSK (Mitomi et al. 1992). Medicinal mushrooms contain a class of polysaccharides known as β-glucans

that promote antitumour immunity. They may act synergistically with some of the new therapeutic antibodies and chemotherapy agents and protect normal marrow (Cheung et al. 2002; Lin et al. 2004). However, in most clinical trials involving cancer patients, the effect on immune functions rather than the blood profile of cancer patients were examined. For instance, in one randomized trial in which lucid ganoderma extract capsules were used on 68 lung cancer patients. Significant increases of total T-cells and NK cells and a slight increase of CD4/CD8 ratios were found in the treatment group compared with the placebo group. The quality of life, in terms of Karnofsky scores, was improved in ~65% of the patients (Gao et al. 2003). Extracts of various medicinal mushrooms can be easily obtained over-the-counter and it is predictable that many patients may use these extracts during their cancer treatments despite the lack of well controlled clinical trials. Although, medicinal mushrooms have been regarded as safe in most TCM practice, recent data has emerged that cautions are needed in using such extracts. In one study, lucid ganoderma extracts were found to be toxic to some human peripheral blood mononuclear cells and this may be significant in patients receiving chemotherapy (Gill and Rieder 2008).

A number of clinical trials, some with randomized controlled design, have been conducted to evaluate the benefits of TCM herbal formulas in patients having chemotherapy. Results of these studies have shown that TCM herbal treatments can reduce the severity of myelosuppression, improve gastrointestinal side effects and increase the patient's appetite. Most importantly, TCM can also increase the probability of patients completing the scheduled chemotherapy that may improve the overall treatment outcome.

One randomized trial recruited 669 patients with late-stage gastric cancer (Yu et al. 1993). One group of patients was treated with herbs that support the spleen and kidney function (Jianpi Yishen Prescription) twice daily for 4–6 weeks with concurrent chemotherapy, while another group was treated with the same type of chemotherapy alone. The combined treatment group showed significantly higher leukocyte and platelet counts with less general and gastrointestinal side effects. The percentage of patients completing the scheduled chemotherapy was 95% in the combined treatment group versus 74% in the chemotherapy alone group ($P < 0.01$).

Zhang (2004) described 47 patients undergoing chemotherapy with a Fuzheng Peiben herbal formula consisted of astragalus root, *Atractylodes lancea* (atractylodes rhizome), *Dioscorea opposita* (Chinese yam), dangshen, Chinese angelica root, white peony root, *Citrus reticulata* (tangerine peel), *Coix lacryma-jobi* (coix seed) and *Bambusa tuldoides* (bamboo shavings). Thirty of the 47 patients (63.8%) managed to maintain normal white cell counts, haemoglobin and platelets counts. There were only 10 patients reported mild symptoms related to chemotherapy. All patients did not experience fatigue and had normal appetite.

It is interested to know that, in another recent double-blind randomized trial where 120 breast and colorectal cancer patients underwent adjuvant chemotherapy were randomized. The treatment group received TCM herbal treatments prescribed by dedicated TCM practitioners according to individualized conditions. The control group received placebo made with similar taste and appearance of common herbal decoction. The study design was intended to have a reasonable representation

of real-life community situation where patients seek their own TCM practitioners to initiate the combined treatment. There was a wide variety of herbal formulas prescribed. All herbs came from a central herbal pharmacy stock where quality assurance was maintained. Results of this study showed no significant difference between the two groups in regards to the chemotherapy associated myelosuppression. Both groups were associated with a moderate incidence of severe (CTC-V2 grades 3 and 4) neutropenia, 52.7% in the TCM group versus 44.7% in control ($P = 0.63$) and leukopenia, 47.3% in the treatment group versus 32.2% in control ($P = 0.37$). Severe anemia and thrombocytopenia were infrequent and the incidence in the two groups was similar. However, there was significant difference in nausea control (Mok et al. 2007).

A Cochrane systematic review of Chinese medicinal herbs for chemotherapy side effects in colorectal cancer patients found some merit in the concoction termed astragalus root compounds (Taixiang et al. 2005). Another Cochrane systematic review of Chinese medicinal herbs to treat the side effects of chemotherapy in breast cancer patients provides limited evidence, even though there was a suggestion of benefit in bone marrow improvement and quality of life (Zhang et al. 2007a).

There were no reported adverse effects since these are rarely documented in Chinese studies that most data have been generated. There are potential detrimental interactions and idiosyncratic toxicity when Chinese herbs and conventional Western pharmaceuticals are used together. Well designed randomized trials, preferably with study endpoints including haematological toxicity parameters and rate of chemotherapy completion, will be necessary to provide the evidence of TCM in decreasing the severity of chemotherapy-induced myelosuppression.

1.5.1.4 Nausea and Vomiting Control and Better Quality of Life

There were a lot of trials with TCM herbal treatments to examine the effects of nausea control during chemotherapy. However, most trials were not randomized and involved small number of patients (Zhang and Fei 2001; Wang and Guan 2004; Jing and Zhang 2005; Mao and Huang 2005).

Mao and Huang (2005) treated 46 patients during chemotherapy with Liujunzi Decoction (Decoction of Six Noble Drugs), a decoction which consists of dangshen, astragalus root, atractylodes rhizome, tuckahoe, pinellia tuber, Chinese angelica root, tangerine peel, *Platycodon grandiflorum* (platycodon root), *Scutellria barbata* (barbat skullcap) and *Paris polyphylla* (herb Paris). Compared with 33 patients who underwent chemotherapy alone, there were only 26% of patients in the TCM group suffered from nausea and vomiting compared with 45% in the control group. Patients in the treatment group also had better sleep and appetite compared to the control group. In another small randomized trial study on 30 patients undergoing chemotherapy for advanced stage colorectal cancer. The treatment group received Da An Pill, which consists of bighead atractylodes rhizome, *Crataegus cuneata* (hawthorn fruit), tangerine peel, *Raphanus sativus* (radish root), *Forsthia suspensa* (weeping forsythia fruit) and other ingredients. Study results showed significant reduction in gastrointestinal discomfort such as nausea and vomiting in the treatment group compared with control (Jing and Zhang 2005).

1.5.1.5 Vasomotor Symptoms Reduction

Vasomotor symptoms with hot flashes and sweating are frequent complications by hormonal manipulative therapies for breast and prostate cancer. Frequent hot flashes with the associated insomnia, fatigue and irritability, were shown to profoundly affect quality of life (Oldenhave et al. 1993). Management of vasomotor symptoms usually involves hormonal replacement therapy with agents like progesterone, megestrol acetate and estrogen or centrally active non-hormonal therapy with agents like gabapentin, antidepressant and venalfaxine (Bordeleau et al. 2007). Chinese herbal treatments may provide an alternative in managing this condition. In TCM perspective, vasomotor symptoms are viewed as kidney deficiencies, blood deficiencies and overactive heart and liver conditions. Correction of these syndrome patterns can result in a reduction of symptoms. Effectiveness of TCM in cancer patients who suffer from vasomotor symptoms has not been studied extensively. Data from non-cancer patients can be extrapolated to study the potential of TCM in treating this condition. However, randomized studies that were reported suffered from poor study design with single herb for the treatment arm. Single herb is rarely used in TCM practice and thus the conclusion from these studies may not be applicable (Hirata et al. 1997; Wiklund et al. 1999).

103 symptomatic women were randomized into treatment and a placebo group in a recently reported randomized study. A TCM herbal formula, Danggui Buxue Decoction (Chinese Angelica Decoction for Replenishing Blood), consisted of a combination of Chinese angelica root and astragalus root was given to the treatment group. Rationale in the choice of this formula was that Chinese angelica root is commonly indicated in treatment menopausal symptoms in TCM and that astragalus root can correct blood and qi deficiencies. Self reported vasomotor symptoms diary and the vasomotor domain of the Menopausal Specific Quality of Life were used to assess outcome for a period of 6 months. Results of this study showed no overall significant difference between the two groups but Chinese Angelica Decoction for Replenishing Blood was found to be effective in treating mild hot flash symptoms compared with the placebo group. The authors suggested that a syndrome patterns diagnosis conducted by TCM practitioners and appropriate herbal treatments may be important than a protocol therapy (Haines et al. 2008).

Keishi-bukuryo-gan (KBG) is a Japanese herbal formula based upon a traditional Chinese medicine formula of the Han Dynasty. This formula is also known as Guizhi Fuling Pill (Pill of Cinnamom Twig and Poria) in Chinese and consists of five herbs: cinnamom twig, tuckahoe, white peony root, *Paeonia suffruticasa* (moutan bark) and peach seed mixed in equal proportion by weight. In Japan, KBG is being widely used as an herbal remedy for hot flashes in post-menopausal women and also in women suffering from hypermenorrhea and dysmenorrea. In vitro studies have shown that KBG has no estrogenic activity. Plasma levels of luteinizing hormone, follicular stimulating hormone and prolactin have not found to be increased by KBG in animal and human studies (Sakamoto 1998; Lerner 2001).

In a recent Japanese pilot trial in 16 prostate cancer patients with hot flushes caused by LHRH agonist, KBG was shown to improve symptoms in 68.8 % (11 out

of 16 subjects) of patients after 4 weeks of treatment. A reduction in the average frequency of hot flash attacks from 5.1 to 3 times per day was observed after KBG treatment. Average duration of flash attack was also reduced from 9.1 to 7.3 min. There was no adverse effect observed in all study subjects (Akihiro et al. 2006). A larger randomized placebo trial is pending to open at the Juravinski Cancer Centre (Canada).

1.5.1.6 Potential for Chemotherapy Cognitive Dysfunction

Chinese herbal therapies may have a role in improving cognitive dysfunction due to chemotherapy. Many patients complain about changes in cognitive function during and after chemotherapy. This phenomenon has been particularly studied in breast cancer patients (Ahles et al. 2003; Tannock et al. 2004). At least 18% of cancer patients who have received standard-dose chemotherapy manifest cognitive deficits on post-treatment neuropsychological testing, and this may be sustained 2 years after treatment (Fan et al. 2005). The patients typically complain of a foggy brain. The impairments have an impact on tests that require sustained attention and speed of information processing. Fatigue and depression are associated disorders. Whether the initial cause of dysfunction is due to loss of neuronal integrity or secondary to metabolic pathology is, as yet, unknown. There may be a genetic component, such as the e4 allele of apolipoprotein (Wefel et al. 2004a). Cytokines, such as interleukin-1 and interferons may play a role, according to some animal experiments (Wefel et al. 2004b). Chemotherapy may damage the endothelium of blood vessels, resulting in thromboses and micro-infarcts in the CNS. Currently, the changes that occur in cerebral tissue after anti-cancer treatments are poorly understood and there are no proven interventions.

Interventions that could ameliorate such disabilities would be of great benefit to the patients and their caregivers. Effects of ginkgo seed extracts have been postulated to include improvement of memory, increased blood circulation, as well as beneficial effects to sufferers of Alzheimer's disease. The most unique components of the extracts are the terpene trilactones, that is, ginkgolides and bilobalide. These structurally complex molecules have been attractive targets for total synthesis. Terpene trilactones are believed to be partly responsible for the neuromodulatory properties of ginkgo seed extracts, and several biological effects of the terpene trilactones have been discovered in recent years. Ginkgolides A, B, C, J, K, L and M and bilobalide are rare terpene trilactones that have been isolated from leaves and root bark of the Chinese ginkgo tree. The compounds were found to be potent and selective antagonists of platelet activating factor (PAF), responsible for their effect on increasing bleeding time. Radioactive isotope studies show cerebral availability, particularly in the hippocampus, striatum and hypothalamus (DeFeudis 2002; DeFeudis et al. 2003; Menku et al. 2003). Lipid peroxidation and brain edema are important factors that produce tissue damage in head injury. An investigation of the effect of mexiletine and ginkgo seed extract (EGb 761) on head trauma of rats showed the usefulness of mexiletine and its combination with EGb 761 as a cerebroprotective agent (Ahlemeyer and Krieglstein 2003). Bilobalide has multiple mechanisms of

action that may be associated with neuroprotection, including its preservation of mitochondrial ATP synthesis, its inhibition of apoptotic damage induced by staurosporine or by serum-free medium, its suppression of hypoxia-induced membrane deterioration in the brain, and its actions of increasing the expression of the mitochondrial DNA-encoded COX III subunit of cytochrome c oxidase and the ND1 subunit of NADH dehydrogenase. As multiple modes of action may apply to bilobalide, it could be useful in developing therapy for disorders involving cerebral ischemia and neurodegeneration (Santo et al. 2003; Bressler 2005). A Cochrane review concludes that it is promising for treating cognitive dysfunction (Kurz and Van Baelen 2004). However, other randomized controlled trials have not confirmed its effectiveness (Dodge et al. 2008). Potential usefulness of ginseng extracts, ginsenosides has also been examined. The ginsenosides can inhibit NMDA receptor-mediated signals (Bao et al. 2005). A combination of ginseng and ginkgo seed was shown to improve cognitive function in normal volunteers (Kennedy et al. 2001). However, further clinical studies on patients with chemotherapy-induced cognitive dysfunction and laboratory studies will be important to explore the potential usefulness of ginkgo seed and ginseng extracts in managing this significant side effects of chemotherapy.

1.5.2 Acupuncture and Related Techniques

1.5.2.1 Reduction of Vasomotor Symptoms

Acupuncture may be able to reduce the vasomotor symptoms associated with anticancer hormone therapy. Many different acupuncture approaches have been tested in non-randomized clinical trials showing a positive reduction in vasomotor symptoms in breast and prostate cancer patients (Hammar et al. 1999; Tukmachi 2000; Cumins and Brunt 2001; Porzio et al. 2002; Filshie et al. 2005; Harding et al. 2009). In one study, 60 prostate cancer patients on luteinizing hormone releasing hormone agonist treatment, were treated with auricular acupuncture using external ear points: autonomic, kidney, shenmen, liver and lung corresponding to the National Acupuncture Detoxification Association protocol for auricular acupuncture. Treatments were given weekly for 10 weeks. 95% of patients reported reduced severity of vasomotor symptoms with a decrease in symptom scores from 5 to 2.1 and $P < 0.01$ (Harding et al. 2009). In another study for 194 breast and prostate cancer patients, an innovative approach of acupuncture treatments given weekly by practitioners to LI4, TE5, LR3 and SP6 and two upper sternal points, but avoiding limbs with lymphoedema or prone to developing it. Patients with no contraindication were instructed to give self acupuncture to SP6 with either semi-permanent needles or conventional needles. Long-term relief of vasomotor symptoms was obtained with 79% of patients gained 50% or greater reduction in hot flushes and 21% with less than 50% reduction (Filshie et al. 2005). These studies suggested acupuncture is a feasible and self approach in managing vasomotor symptoms in cancer patients. In recent years, several randomized trials were reported. These trials compared various

acupuncture approaches with or without other interventions versus placebo or self care in cancer and non-cancer patients with vasomotor symptoms (Zaborowska et al. 2007; Frisk et al. 2008; Borud et al. 2009). However, two systematic reviews on the randomized trials of acupuncture for vasomotor symptoms concluded that there is no strong evidence to support the effectiveness of acupuncture (Cho and Whang 2009; Lee et al. 2009). This confusing conclusion is probably due to the absence of rigorous randomized controlled trial with larger enough patients number and the lack of suitable placebo. Further research with robust study design is required to adequately examine the usefulness of acupuncture in vasomotor symptoms.

1.5.2.2 Chemotherapy-induced Peripheral Neuropathy

Besides bone marrow suppression, bowel and renal toxicities, neurotoxicity is often a dose limiting side effect that leads to necessary reduction of chemotherapy dose or even termination of therapy. Chemotherapy-induced peripheral neuropathy (CIPN) appears to occur in 10–20% of patients (Forman 1990). The frequency of this often debilitating toxicity is increasing because of the ability to dose-escalate chemotherapy through improvements in supportive care. Many chemotherapy agencies including platinum compounds, vinca alkaloids, taxols and suramin can cause neurotoxicity. Different components of the peripheral nervous system can be affected resulting in neuropathy. CIPN is most frequently associated with axonal degeneration and a dying-back type of neuropathy. Commonly this occurs weeks to months after exposure to the drug and may continue despite withdrawal of the drug (Kaplan and Wiernik 1982). Symptoms of neurotoxicity can appear immediately during or after the course of chemotherapy and its severity depends on the type and the accumulative dose of chemotherapy used. Sensory or sensory-motor peripheral neuropathy is the predominant presenting symptom while autonomic nervous system dysfunction can occasionally be seen. Patients usually present with continuous or intermittent pain that is described in terms of burning, shooting or electric, and most patients describe more than one pain. Patients may report abnormal pain to normally painful or non-painful stimuli, and may report sensations such as itching, numbness, pins and needles, and tingling. Impaired vibration and joint position sense, ataxia, myalgia and muscle weakness may occur depends on the types of nerve fibre affected. Although damages to the peripheral nerve may recover in most patients, the recovery is incomplete resulting in persistent symptoms (Martin and Hagen 1997). Unrelieved pain can impact patients' functional abilities and severely affecting patient's quality of life.

Current treatments of CIPN are aimed for symptomatic relief of paraesthesia and pain. Tricyclic antidepressant, ion channel blockers: carbamazepine and gabapentin have been shown to be moderately effective, but side effects associate with these medications including sedation, postural hypotension, dry mouth and cardiac problems make their usage limited and may not be acceptable to patients. Moreover, symptoms reappear after these medications are discontinued (Sindrup and Jensen 1999; Quasthoff and Hartung 2002). Thus, better treatments for this debilitating chemotherapy induced peripheral neuropathy are continuously being explored.

Treatment for patients with symptoms consisted of paraesthesia, hyperalgia, pain, pin and needles presenting in both feet and hands have been described in TCM Classics (Flaws 1999). In TCM model, symptoms presented in CIPN are considered to be a state of deficiency in qi and blood and the body's failure in directing these components to the four limbs leading to sensory symptoms and impaired limbs function. Successful treatment with acupuncture has been described based on an approach by improving body qi and blood and directing flow to the extremities. In recent published clinical trials, acupuncture treatment has been shown to induce significant symptom improvement in patients with peripheral neuropathy due to HIV or diabetes mellitus (Phillips et al. 2004; Abuaisha et al. 1998). At Juravinski Cancer Center, a pilot trial was conducted using an acupuncture protocol for patients with CIPN caused by combined taxol and platinum treatments for gynaecological cancers (Wong and Sagar 2006). In this trial, 5 consecutive patients (60–71 years old) with greater than WHO grade II CIPN symptoms were recruited. All received carboplatinum and taxol chemotherapy. Duration of symptoms before acupuncture treatment ranged from 6 to 38 months (median 18 months). 3 patients had Grade II and 2 had Grade III symptoms. Pain, numbness and tingling of fingers and toes were the chief symptoms in all patients. Imbalance in gait was seen in 3 patients. Average pain score was 7.8/10 (range from 6 to 9). At the end of the two courses of acupuncture treatment using a structured protocol, all 5 patients reported improvement of pain, numbness and tingling. Average pain score was 3/10 (range 1–5). Symptoms improvement was seen after first treatment for the patient with 6-month history of CIPN symptoms. All patients had a reduction in analgesic dosage. Gait imbalanced was significantly improved in all 3 patients. At 6 months follow-up, symptoms improvement persisted in 4 patients. One patient with history of diabetes and multiple sclerosis reported symptoms improvement for 1 month only. Although the number of patients studied was small, the results suggest potential usefulness of acupuncture treatment in CIPN and further trials of larger number of patients with more formal assessment is needed. An ongoing Phase II trial using the same acupuncture protocol for CIPN is currently underway at the Juravinski Cancer Centre (Canada).

1.5.2.3 Reduction of Chemotherapy-induced Nausea and Vomiting

Usefulness of acupuncture for nausea and vomiting has been established based on positive results from trials discussed in previous sections. A Cochrane Database systematic review specifically on acupuncture point stimulation using all methods for chemotherapy-induced nausea or vomiting was conducted recently. The conclusion of the review suggested that electroacupuncture is effective and that acupressure can reduce acute nausea but non-invasive electrostimulation is not beneficial. However, the clinical relevance of acupuncture for this condition remains questionable since there is no well conducted study examining the additional benefit of a combination of electroacupuncture with state-of-the-art antiemetics. The management of patients with refractory symptoms is also important to be examined (Ezzo et al. 2006).