Chemotherapy-Induced Peripheral Neuropathy

Chinese Herb Approach Based on a Modified Ancient Formula

by Subhuti Dharmananda, Ph.D., Director, Institute for Traditional Medicine, Portland, Oregon

One of the tenets of traditional Chinese medicine (TCM) is that many of the ancient formulas have extremely valuable clinical effects and can be used today for patients who present similar symptom patterns despite markedly different initiating causes of those symptoms. This kind of adaptation of formulas should be subject to careful evaluation, a difficult and time consuming task if the procedure is to be done properly. TCM doctors working in China (or other nations were this kind of medicine is practiced, such as Korea and Japan) frequently use the ancient prescriptions as their starting point for dealing with modern health care problems; some practitioners keep the ancient formulas as described in the past, and others, perhaps the majority, modifying the formula to take into account more recent developments in TCM itself and in knowledge of the disease being treated.

In the case of chemotherapy-induced peripheral neuropathy (CIPN), this condition has been brought to the attention of TCM doctors only since the widespread introduction of chemotherapy in China, which can be traced to the 1960s with then widely-used vinca alkaloids and a few other drugs, developed in China but not used internationally. This adverse effect of chemotherapy is an ongoing concern. Diabetic peripheral neuropathy, which has a different underlying cause but a similar manifestation, is something that has been around a much longer time, though having been less prevalent in the past than now. In China, as elsewhere, people of wealth and power were often freed of manual labor and had access to plentiful food, two factors leading to obesity and diabetes. So, treatment of diabetic peripheral neuropathy serves as a point of earlier experience that may have some bearing on the issue of neuropathy that develops from non-diabetic initiators, such as cancer chemotherapy.

Certain chemotherapy drugs have a higher propensity than others to cause neuropathy and the ones most extensively used and known to cause this effect are the platins, such as cisplatin, carboplatin, and oxaliplatin. These are compounds utilized for administering the heavy metal platinum, which strongly inhibits cancer cell reproduction via DNA cross-linking, but also has a neurotoxic effect on peripheral nerves, while central nerves are protected by the blood-brain barrier. The particular result is usually called sensory neuropathy, which has presentation of numbness, tingling, and pain. The platin drugs were introduced about 45 years ago, starting with cisplatin, and new versions are developed especially to better treat certain cancer cell origins, as well as to minimize development of tumor cell resistance to the drug. Somewhat more recently, the taxanes, derivatives of a compound found in *Taxus* trees (Yew trees), have been utilized especially for advanced cancers and have a high level of peripheral neuropathy side effect. Pharmacologic control of CIPN, but not prevention, is based on using pregabalin (Lyrica), amitriptyline, and gabapentin, among others.

Several natural products, or synthetic versions of the original compounds, have been suggested for help with this side effect, though none have reached a level of evidence to result in recommendation by oncologists; among them: B vitamins (especially B1 and B12), omega-3 fatty acids, alpha-lipoic acid, calcium/magnesium, and selenium. Natural health care approaches for minimizing CIPN ran into a stumbling block when one therapeutic agent, the amino acid carnitine, was applied as acetyl-carnitine for patients utilizing the main taxane drugs (Paclitaxel, Docetaxel). In a clinical evaluation reported in 2013, this supplement appeared to make matters worse rather than better (more patients with CIPN and more patients with more severe CIPN). While one can challenge these findings, for example, because the frequency of CIPN was unusually low overall so as to yield coincidental circumstances affecting the results, the study findings raised a caution that has been difficult to overcome. Carnitine is produced by the body and is obtained in the diet from animal-based products (hence its name, based on *carni*), and would thus seem to be safe. The majority of studies of natural substances given for CIPN, including herbs, indicate that they do not appear to cause adverse consequences, while proof of the efficacy claimed will depend on more stringent studies.

The ideal situation for the TCM practitioner is to begin treating the cancer patient as chemotherapy is initiated, rather than after neuropathy has developed, as it remains unclear to what extent CIPN can be reversed. In order for cancer patients to consider going to a practitioner of Chinese medicine, there needs to be a significant amount of experience in this field to provide some level of confidence.

Turning to Ancient Formulas

TCM doctors who work with the **Shang Han Lun** and **Jin Gui Yao Lue** as primary texts point to the sixth chapter of **Jin Gui Yao Lue** when it comes to diabetes-caused neuropathy. This chapter is about two syndromes: Xue Bi (Blood Numbness; meaning numbness associated with depletion of blood; the term bi can point to several types of distress, including pain) and Xu Lao (Weakness Fatigue; meaning a person with constitutional deficiencies or persistent weakness who suffers from substantial fatigue after any exertion). There is some overlap, in that the emphasis for both syndromes is what happens when the person is fatigued. For the topic of concern here, Blood Numbness is the one that has been deemed to fit with the consideration of CIPN and also diabetic neuropathy. There are only two passages on this subject and they initiate chapter 6. The first passage appears to be a contribution of the Wang Shuhe, the author of the **Mai Jing** (Pulse Classic), who had preserved the **Shang Han Lun** and gathered parts of the **Jin Gui Yao Lue** (hereafter, **Jin Gui**). Wang had received a damaged copy of Zhang's original works, and put together both the original information that he could pass on and provided introductory and explanatory passages that he thought filled in for what should have been there. Wang's style of writing is based on disciples asking questions of their master; because of his focus on pulse, he usually added pulse information beyond what Zhang may have indicated or, at least, he modified it to his style of description. The second passage of chapter six of the **Jin Gui** appears to be primarily a direct contribution of Zhang, who, by contrast to Wang, typically just gave the disorder's description and which formula to use.

Here I present the translation of this segment of the **Jin Gui** that was provided by the Oriental Healing Arts Institute (OHAI), published in English in 1983, and based on a Taiwanese text that was in standard use. As a result of cultural context and date for this Chinese language original, it is not influenced by modern TCM as is the case in translations from mainland China. The English language expressions used are sometimes archaic, and not the ones we would likely choose today. Thus, Blood Numbness is called in the translation Blood Paralysis, even though we consider paralysis to refer to inability to move (which is not the description of the text) and the description of "thick flesh" (some others translate as exuberant flesh), in this version is voluptuous, while we tend to reserve the latter term for a more specialized application. While this translation rightly depicts "non-active individuals," a more direct translation would indicate that these individuals have a life that allows for avoiding labor. For terms not translated to English, the transliteration method in the OHAI text is Wade-Giles, but I rendered these in pinyin for easier reading by those who have now learned pinyin. Nonetheless, the translation overall is good:

> The disciples asked: "What causes blood paralysis?" The master said: "It usually occurs in non-active individuals with voluptuous bodies and weak bones. When fatigued, they sweat and turn frequently during sleep thus exposing their skin to slight drafts. If the pulse is minute and harsh on the cun site and thin and tense of the guan site, it is appropriate to activate yang qi by acupuncture in order to soften the harshness and to relax the tenseness, thus bringing about recovery.
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> The patient suffering from blood paralysis with a minute pulse palpable both superficially and deeply on the cun and guan sites, a thin and tense pulse on the chi site, and an external conformation exhibiting generalized numbness like that of wind paralysis should be principally treated with Huang Qi Gui Zhi Wu Wu Tang.

The OHAI text then includes the list of the formula's ingredients and their method of preparation, a description likely provided during the Song Dynasty when the **Jin Gui** we have today was compiled and edited; here is the OHAI translation:

3 taels Huang Qi
3 taels Shao Yao
3 taels Gui Zhi
6 taels Sheng Jiang
12 fruits Da Zao

Decoct the ingredients in 6 sheng of water until 2 sheng remains; seven-tenths sheng warmed is taken three times a day. A similar formula from another source also includes ginseng as an ingredient.

A tael is also known as a liang, which is ten qian. But, we don't really know how these measures translate today. A common method of interpretation is to adjust tael or liang to today's qian, which is about 3.1 grams, making 3 taels about 9 grams. Thus, the formula might be 9 grams of each of the first three ingredients, 18 grams of Sheng Jiang (which is a fresh product rather than dried) and about 12 grams of Da Zao, the weight of these fruits after removing the pits. The instruction to use 7/10 of a sheng is just an expression for taking one-third each time of the 2 sheng portion. A sheng was probably around a six ounce portion (so, 6 sheng would be about 36 ounces or four and a half cups). The brief mention of "a similar formula" was a commentary from some later author and doesn't seem to have any implications attached to it; this comment is not found in most modern translations. The rather small amount of information presented here is the entire discussion of Xue Bi. There is passing mention of "wind paralysis" (Feng Bi), which is depicted elsewhere as combining numbness and pain, while Xue Bi is the numbness but little or no pain.

The reference to thick flesh can mean a substantial muscle mass, presumably flabby due to lack of activity, and the term does not necessarily mean fat; weak bones would not be a reference to osteoporosis, but a general weakness of the limbs, as someone who has difficulty walking, maybe shuffling along, a condition depicted as the bones being weakened or as weakness of bones and tendons. The issue of sweating, fatigue, and wind will be discussed later in this article.

The **Shang Han Lun** has a dominant formula, Gui Zhi Tang (Cinnamon Combination), and there is an extensive range of modifications of it, some arrived at by removing or adding ingredients and/or adjusting the proportion of an ingredient while leaving the others the same. The **Jin Gui** carries over many of these Gui Zhi Tang formulations and adds a few more. This formula for Xue Bi, Huang Qi Gui Zi Wu Wu Tang (Decoction of Five Substances led by Astragalus and Cinnamon), is one of them, with removal of Zhi Gan Cao from Gui Zhi Tang and replacement of it with Huang Qi, while doubling the dose of Sheng Jiang.

A formula derived from Gui Zhi Tang to which Huang Qi is added, with no change in the quantities of other ingredients (i.e., Sheng Jiang is not increased) is in the **Jin Gui** chapter 14, called Gui Zhi Jia Huang Qi Tang. The purpose of this formula is to induce sweating (same as the case with Gui Zhi Tang). The formula is mentioned after a long and complex description of a health problem in the category of yellow sweat disease, within the broader category of water diseases that are addressed in this chapter. Some aspects of the condition elucidated there seem relevant to the matter at hand and will be pulled out from the larger description:

Yellow sweat disease often causes chilling of the tibia…if a patient perspires after eating, sleeps at dusk, and has night sweats, he is suffering from fatigue and qi exhaustion…

There is no mention of numbness, but perspiration, sleeping, and fatigue all enter in. Here there is reference to "chilling of the tibia," referring to the main bone of the lower leg; not intending to mean that the bone itself somehow becomes cold, but that the meridians running through this portion are influenced by cold. The description for the formula Gui Zhi Jia Huang Qi Tang does mention "sensation as though something were under the skin" and "heavy feeling," and these may refer to a neurologic manifestations that overlap with the designation of numbness for the Xue Bi formula.

Going back to chapter six, in the section of Xu Lao, there is another modified Gui Zhi Tang with Huang Qi called Huang Qi Jian Zhong Tang (meaning: Astragalus Support the Middle Decoction, referring to the

spleen/stomach as middle). This is said to be made by adding 1.5 taels of Huang Qi to Xiao Jian Zhong Tang, which is Gui Zhi Tang with double Shao Yao and with the addition of a sheng measure of maltose, Yi Tang, a grain-derived sugar in thick syrup form. The role of Yi Tang is to alleviate distress as well as strengthen the stomach/spleen via the sweet taste.

This Gui Zhi Tang derivative prescription is indicated for "weakness fatigue, internal cramps, and deficiencies of various types" while the base formula it is organized around, Xiao Jian Zhong Tang is indicated for those symptoms and some others, including "soreness and aching in the extremities." Thus, there is another connection between fatigue and uncomfortable sensation in the extremities.

Huang Qi is not used in the **Shang Han Lun** and only infrequently in the **Jin Gui**, mainly an ingredient of formulas in these two chapters (6 and 14). It is difficult to assess the specific role of Huang Qi, but the indication for "deficiencies of various types" added to the description of the formula without Huang Qi does point to its overall tonification effect. Its use in several formulas in the chapter on water disorders (14), such as for a condition of water swelling of the skin, would point to it as having an effect of removing water accumulations. The formula with the largest amount of Huang Qi in these ancient prescriptions is called Huang Qi Shao Yao Gui Zhi Gu Jiu Tang, comprised of the three herbs mentioned in the title: Huang Qi at 5 taels, plus Gui Zhi and Shao Yao at 3 taels each. This is described as a treatment for yellow sweat in the situation where if one takes a bath while perspiring, the bath water invades the surface of the body via the pores and causes yellow sweat. Modern explanations for yellow sweat (a symptom rather than disease pattern), as may have occurred in ancient times, would be a bacterial skin infection that mixes with substances in the sweat glands; as in the case of the bath water invading the body through the pores. The bath water used at the time this yellow sweat disorder occurred might have been non-sterile, and served as a source of contamination of the sweat glands.

Huang Qi was also known in ancient times to treat stagnation at the body surface, and in the instance of numbness, the condition is thought to manifest primarily at the surface (skin and muscle). The addition of an extra quantity of fresh ginger in Huang Qi Gui Zi Wu Wu Tang may imply an intention to have greater warming effect, especially for coldness in the stomach/spleen, displayed by the pulse that is thin and tense at the guan site (middle position of the right pulse at the wrist) and the extra Shao Yao in Xiao Jian Zhong Tang may be intended to help relieve cramps, which it is especially effective for when combined with Zhi Gan Cao.

One could reasonably expect that the three formulas with Gui Zhi Tang as the base and Huang Qi added would all be suitable for protecting the nerves from damage if any one of those formulas is; that is, one of them is not necessarily more specific for such an application than the others, apart from the limited mention of numbness. Still, because of its prominence in chapter 6 and focus on numbness, the formula Huang Qi Gui Zhi Wu Wu Tang has been selected. Using the reasoning that is presented here, this formula was first considered suited for diabetic neuropathy, and this has been such a frequent choice of prescription that a study was done of literature reports on its application (Huangqi Guizhi Wuwu Decoction for treating diabetic peripheral neuropathy by Pang Bing, et. al., Neural Regeneration Research 2016, 11(8): 1347-1358; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5020836/). The reviewers found a number of publications mentioning this application of the formula, but they were seeking the modern randomized controlled studies, of which they found 16 (there were, to give an example of excluded literature, about 50 case reports or retrospective evaluations). All of the 16 studies utilized a modified version of the **Jin Gui** formula rather than the original. The formula modifications were not disclosed in the review article. Only two of the studies utilized a true placebo, the rest used for the control group vitamin B12, 500 µg per dose, either once per day or three times per day.

In one article, Efficacy of Chinese Herbal Medicine in the Treatment of Moderate-Severe Painful Diabetic Peripheral Neuropathy: A Retrospective Study (Journal of Diabetes Research, 2019), for which a translation was available in English, it was pointed out that each patient would get adjusted formulas according to presentation and the dose of individual ingredients could also vary, but a typical base formula would be:

Huang qi: 30 grams
Gui zhi: 15 grams
Bai Shao: 15 grams
Gan Cao: 15 grams
Ji Xue Teng: 30 grams
Ye Jiao Teng: 30 grams

Note that two original ingredients of Huang Qi Gui Zhi Wu Wu Tang are not included: Sheng Jiang and Da Zao. As a general observation, these two herbs, which are found in numerous formulas of the **Shang Han Lun** and **Jin Gui** are frequently left out of modern adapted versions of the ancient formulas for a variety of applications. The key additions are Ji Xue Teng (millettia; spatholobus) and Ye Jiao Teng (polygonum stem; this is the stem of the plant yielding He Shou Wu), two blood nourishing, blood vitalizing agents from different botanical sources but with similar uses.

In the Chinese Journal of Integrative Medicine, volume 12, number 1 (March 2006), there is an article Clinical Study of Jiawei Huangqi Guizhi Wuwu Decoction in Preventing and Treating Peripheral Neuro-sensory Toxicity Caused by Oxaliplatin, by Li Yuan, Cui Huijuan, Huang Jinchang, et. al. While the study, as expected from Chinese herbal literature, yielded a positive result in preventing neuropathy from oxaliplatin, the interesting part of the article is the formulation, which I am here designating as Anti-CIPN Formula:

Huang Qi: 15 g
Gui Zhi: 10 g
Bai Shao: 15 g
Da Zao: 10 g
Fu Ling: 12 g
Dang Gui: 12 g
Ji Xue Tang: 15 g
Xi Xian Cao: 15 g
Zhe Chong: 3 g
Chi Shao: 15 g

These doses are for a one day administration, divided into two portions. This is 120 grams of herbs, characteristic of modern TCM prescribing. Note the use of some herbs not mentioned in **Jin Gui** (such as Ji Xue Teng and Xi Xian Cao), and the relatively high total dose due to doubling the number of ingredients from five to ten. It should be noted that here, too, Sheng Jiang has not been included, and the authors do not mention this herb when describing the traditional formula of five herbs for which they do specify the other four. In the discussion section, each of the four remaining herbs of the traditional prescription are described in terms of their actions, with no mention of Sheng Jiang. The authors give an explanation of the formula modification: “The newly added herbs increased the function of warming and activating yang to stimulate meridian and promote blood circulation to relieve numbness or pain.” To make this formula today, since Zhe Chong (a beetle) is no longer permitted in the U.S., a substitute blood-vitalizing herb may be utilized; as an example, 10 grams of Ru Xiang (frankincense) might be used in its place, as this resinous material is also indicated for numbness.

Original Concept

The disorder originally described in the **Jin Gui**, as quoted earlier, has this background: “It usually occurs in non-active individuals with voluptuous bodies and weak bones. When fatigued, they sweat and turn frequently during sleep thus exposing their skin to slight drafts.” This description follows a framework that was prevalent in the early centuries of traditional Chinese medicine: that a major cause of disease is from penetration of wind into open pores when there is any weakness that can allow the wind to penetrate further. The concept of wind at that time was quite complex and somewhat obscure, in that its ability to have adverse influence was based on an understanding of evil influences moving about with the wind. In particular one

did not need to be out in gusty wind, in fact, that kind of wind is so disturbed that it carries little influence on the body, rather a tiny draft was sufficient to cause disease when the person is in a receptive state. There is a well-known story in ancient China that may have even been behind the description here for blood paralysis. It goes like this: there was an elderly gentleman who for dinner ate ravenously a rich meal and consumed much wine. Afterward, he felt tired and sat in his rocking chair resting, perspiring somewhat from the effects of the food and drink. His home was not in good repair, and there were some cracks in the walls. Through these cracks passed a tiny breeze, and as it encountered him, the draft entered his pores and proceeded to penetrate to the center, causing his circulation to seize up and he died.

The cause of death would be categorized today as heart attack or stroke, and we might consider with modern medical ideas that the heavy meal, on top of prior conditions, led to an obstructed artery, with the perspiration and cracks in the wall having nothing to do with his cardiovascular event. From the TCM point of view, however, there is a specific initiating cause of the event. This gentleman who suffered such consequences may have been eating rich foods for years on end with nothing happening as a result. What happened to him this night was the combination of the opening of his pores while in a state of some debility, tiredness or fatigue, and the cracks in the wall letting in a small circulation of the air, with its adverse influences carried intact. In the **Jin Gui** depiction, there is a generalized circumstance, rather than reference to an individual event, but the individual has been eating too much, not exercising, and has become weak, and with weakness, the pores tend to open easily. When a person with such background becomes fatigued, such as from working too much or eating too much, they are tossing and turning at night, and exposing different parts of the body to any drafts that might be present. The idea is that parts of the body get uncovered, and by tossing and turning, the most susceptible area gets exposed. Eventually, then, they will suffer the effect of this adverse wind entering their pores, encountering little resistance because their qi and blood doesn't fill the vessels at the surface, and, in this case, penetrating just below the skin to produce numbness. The main site of the numbness will be in the limbs, which is where the manifestation of "weak bones" is usually experienced.

The formula Gui Zhi Tang is one affiliated with perspiration; the patient selected to receive the formula is perspiring slightly and the formula is intended to induce further perspiration. This may seem a contradiction, but in the **Shang Han Lun** description, the initial perspiration is from the disease condition (a mild fever with sweating) but it is not sufficient sweating to get rid of the disease by purging the adverse influence back out through the pores. The induced perspiration becomes necessary, intended to force the pathogenic influence out, but not so much as to weaken the person further and permit the disease to overwhelm the defenses and penetrate further. In the opening of the **Shang Han Lun**, the condition calling for Gui Zhi Tang is a "greater yang" disease (tai yang); the mild form of this disease is called Zhong Feng (penetrating wind) while the more severe from is called Shang Han. For the blood paralysis condition, the initial recommendation in the text is to activate yang qi with acupuncture, and then also with herbs, modifying Gui Zhi Tang with increased Sheng Jiang and addition of Huang Qi.

The numbness that arises in the case relayed by the ancient text likely differs from the chronic numbness of peripheral neuropathy as we know it. The modern TCM practitioner adjusts the ancient formula in accord with the manifestation of a prolonged symptom, appearing continually in the same location, a factor which is frequently interpreted as showing the presence of blood stasis. Numbness itself is considered a consequence of dampness accumulation and stagnation. Therefore, modern treatments may add emphasis to the therapeutic actions of resolving damp (e.g., add Fu Ling) and vitalizing blood (e.g. add Ji Xue Teng), while further nourishing blood to help overcome the deficiency that gave rise to a "blood paralysis" (e.g., add Dang Gui).

The modified versions of the traditional formula are often called Jia Wei Huang Qi Gui Zhi Wu Wu Tang (or using proper pinyin: Jiawei Huangqi Guizhi Wuwu Tang; abbreviated JHGWT). These versions may be employed in the effort to overcome peripheral neuropathy as caused by short term exposure to chemotherapy drugs, such as the platins and taxanes.

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