

Chemotherapy and Chemo-Support

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The purpose of treating cancer cells with chemotherapy is to prevent them from dividing, invading and metastasizing. Most chemotherapeutic agents exert their effect on cell multiplication: obviously since multiplication is a characteristic of many normal cells, chemotherapeutic agents will inevitably affect also normal cells and especially those with a rapid rate of multiplication and turnover such as those of the hair, intestinal mucosa, blood and bone marrow. This explains the common toxic effect of chemotherapy on the hair, the intestines (vomiting and diarrhoea), the blood (affecting blood counts) and bone marrow (affecting the immune system).

Inhibition of cell multiplication can take place at several levels within the cell:

- Macromolecular synthesis and function
- Cytoplasmic organization
- Cell membrane synthesis function
- Environment of cancer cell growth

Most agents have their primary effect on either macromolecular synthesis or function. They interfere with the synthesis of DNA, RNA or proteins or with the appropriate functioning of the molecule. When interference with macromolecular synthesis or function of the neoplastic cells is sufficiently great, a proportion of the cells die. Because only a proportion of the cells die as a result of a given treatment, repeated doses of chemotherapy must be used to continue to reduce their number.

Neoplastic cell death may not take place at the time of exposure to the chemotherapeutic agent. Often the cell must undergo several divisions before the lethal event that took place earlier results in death of the cell. This means that the effect of chemotherapy may last for several weeks after the end of the treatment: likewise with its toxic effects on normal cells. This has important implication for our protocols as it means that we need to continue tonifying Qi and Blood for some time after the end of the treatment.

TOXICITY

The toxicity of chemotherapeutic agents (and also of other drugs) is not a fixed entity but it varies according to several factors:

- Toxicity of specific agent
- Dose
- Schedule of administration

- Route of administration
- Predisposing factors of the patient which may be known or unknown before the start of the treatment
- Sex (women tend to develop toxicity at a lower dose than men)

Common Toxicities

Some toxicities are relatively common among chemotherapeutic agents. Common acute toxicities include:

- Myelo-suppression with leukopenia, thrombocytopenia and anaemia.
- Nausea and vomiting
- Mucous membrane ulceration
- Alopecia

Apart from nausea and vomiting, these toxicities occur because of the cytotoxic effect of chemotherapy on rapidly-dividing normal cells in the bone marrow, mucous membranes and hair.

The side-effects of chemotherapy vary greatly according to the agent used. Agents may be broadly classified into four groups:

- **Alkylating agents** damage the programs that control growth in the chromosomes of the tumour cells. Example: busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, estramustine, ifosfamide, lomustine, mechlorethamine, melphalan, semustine, thiotepa.
- **Antimetabolites** interfere with the manufacture of nucleotides, the substances that make up the DNA. Example: azacitidine, capecitabine, cladribine, floxuridine, fludarabine, 5-fluorouracil, gemcitabine, mercaptopurine, methotrexate, pentostatin, raltitrexed, thioguanine, trimetrexate.
- **Natural products** interfere with cell structure and cell division. Example: asparaginase, bleomycin, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, idarubicin, irinotecan, plicamycin, mitomycin, mitoxantrone, taxol, teniposide, topotecan, vincristine, vinblastine.
- **Hormones** block the effect of oestrogen by acting on the oestrogen-receptors. Example: aminoglutethimide, anastrozole, bicalutamide, dexamethasone, diethylstilbestrol, fluoxymesterone, flutamide, goserelin, leuprolide, letrozole, nilutamide, raloxifen, tamoxifen, torenufen.
- **Miscellaneous agents**: altretamine, amifostine, amsacrine, dexrazoxane, hydroxyurea, mitotane, pamidronate, porfimer, procarbazine.
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- **Biologic agents**

Monoclonal antibodies: rituximab, trastuzumab.

- Interferons: interferon- γ 2a and interferon- γ 2b.
- Interleukins: aldesleukin, oprelvekin.
- Myeloid- and erythroid-stimulating factors: erythropoietin, filgrastim, sargramostim.

Short Term Side Effects of Cytotoxic Drugs

Short-term side-effects of cytotoxic drugs include:

- Loss of appetite
- Nausea
- Vomiting
- Stomatitis
- Malaise
- Flu-like feeling, fever
- Cystitis
- Haematuria
- Constipation
- Diarrhoea

Long Term Side Effects of Cytotoxic Drugs

Long-term side-effects of cytotoxic drugs include:

- Cardiac toxicity (usually from high doses of doxorubicin or daunorubicin). Doxorubicin is widely used for breast carcinoma. If radiation is administered to the chest, the cardiac toxicity (in the form of congestive cardiac failure) may occur at lower doses. This particular long-term side-effect may occur even several years after the administration of chemotherapy.
- Pulmonary toxicity (pulmonary fibrosis) is associated with high doses of bleomycin but also with alkylating agents and methotrexate.
- Haematologic impairment. Alkylating agents may cause cytopenia.
Immunologic impairment and myelo-suppression. Fludarabine, cladribine and pentostatin cause profound suppression of CD4 and CD8 lymphocytes and render patients treated susceptible to opportunistic infections. There may be a fall in white blood cells and platelets counts.
- Skin reactions (rash, inflammation, pigmentation, photosensitivity)
- Liver toxicity.
- Nephrotoxicity. This is typically caused by cisplatin, oxaliplatin, methotrexate and nitrosoureas). This toxicity may be acute or chronic and in severe cases it may require haemodialysis.
- Neurotoxicity (peripheral neuropathy) is typically caused by vinca alkaloids, cisplatin, oxaliplatin, epipodophyllotoxins and paclitaxel.
- CNS toxicity (lethargy, fatigue, depression, headaches, poor memory and concentration)
- Premature menopause may occur in women who have received certain chemotherapeutic agents such as alkylating agents or procarbazine.

Side Effects of Individual Cytotoxic Drugs

- **Adriamycin**
- Heart muscle damage, haematuria, hair loss, nausea, vomiting, mouth ulcers.
- **Anthracyclines**
- Cardiomyopathy.
- **Asparaginase**
- Anaphylaxis (allergic reaction), fever, malaise.
- **Bleomycin (or Blenoxane)**
- Alopecia, stomatitis, fever, skin reactions, nail ridging, pulmonary toxicity.

- **Carboplatin (or Paraplatin)**
- Nausea, vomiting, bone-marrow suppression, nephrotoxicity, liver function abnormalities, diarrhoea.
- **Chlorambucil**
- Myelo-suppression, amenorrhoea, azoospermia, CNS effects at high doses.
- **Cisplatin**
- Nausea, vomiting, diarrhoea, bone-marrow suppression, renal toxicity, neurotoxicity, ototoxicity, severe electrolyte abnormalities (hyponatremia, hypomagnesemia, hypocalcemia, hypokalemia), peripheral neuropathy.
- **Cladribine**
- May cause profound suppression of CD4 and CD8 lymphocytes, nausea, skin rash, fever, headache, myalgia, arthralgia.
- **Cyclophosphamide**
- Bone-marrow suppression, hair loss, nausea, vomiting, cystitis, haematuria.
- **Dacarbazine**
- Severe nausea and vomiting, flu-like feeling, malaise, diarrhoea, bone marrow suppression.
- **Daunorubicin**
- Myelo-suppression, cardiac toxicity, nausea, vomiting, alopecia.
- **Doxorubicin**
- Nausea, vomiting, stomatitis, hair loss, bone-marrow suppression.
- **Epipodophyllotoxins**
- Neuro-toxicity (peripheral neuropathy).
- **Etoposide**
- Nausea, vomiting, hair loss, bone-marrow suppression.
- **Fludarabine**
- May cause profound suppression of CD4 and CD8 lymphocytes, nausea, vomiting.
- **5-Fluorouracil**
- Diarrhoea, mild nausea, stomatitis, bone-marrow suppression, painful, erythematous desquamation and fissures of palms and soles.

- **Ifosfamide**
- Bone-marrow suppression, nausea, vomiting, cystitis, renal toxicity.

- **Melphalan**
- Renal toxicity, nausea, vomiting, diarrhoea, hair loss, stomatitis, bone marrow suppression, depression.
- **Methotrexate**
- Bone-marrow suppression, nausea, stomatitis, skin reactions.

- **Methotrexate** (high dose)
- Mouth ulcers, stomach ulcers, nausea, vomiting, bone-marrow suppression, renal toxicity.
- **Mitomycin-C**
- Nephrotoxicity, bone-marrow suppression.
- **Mitoxantrone**
- Mild nausea and vomiting, loss of appetite, mild hair loss, bone-marrow suppression.
- **Paclitaxel**
- Neuro-toxicity (peripheral neuropathy), myelo-suppression, nausea, vomiting, alopecia.
- **Pentostatin**
- May cause profound suppression of CD4 and CD8 lymphocytes.
- **Procarbazine**
- Food and drug interactions (it has a MAOI activity and patient should avoid beer, wine, fermented cheese, chocolate, fava beans and yeast extracts), myelo-suppression, nausea, vomiting, rash, hives, photosensitivity.
- **Taxol**
- Bone-marrow suppression, allergic reaction, neurological damage, nausea, vomiting, diarrhoea.
- **Thiotepa**
- Fatigue, nausea, vomiting, cystitis, dizziness.
- **Vincristine**
- Constipation, numbness, tingling, paraesthesia of hands and feet.

Chemotherapy Side Effects from the Point of View of Chinese Medicine

If we analyze the above side-effects, there are important differences between various cytotoxic drugs and one could conceivably formulate an individual Chinese herbal formula for each. However, one can identify common characteristics among the above side-effects. We can attempt to group the side-effects according to the Chinese pathological pattern induced by the various cytotoxic drugs. Looking at the side-effects of each drug, four patterns in particular stand out:

1. DEFICIENCY OF QI, BLOOD AND YIN

Hair loss, diarrhoea, nail ridging, bone-marrow suppression, malaise, fatigue, depression, loss of appetite, neurological damage, dizziness, constipation, numbness, tingling, paraesthesia of hands and feet.

2. ST-QI REBELLING UPWARDS

Nausea, vomiting.

3. STOMACH HEAT

Mouth ulcers, stomatitis, stomach ulcers.

4. BLOOD HEAT

Haematuria, fever, skin reactions, cystitis.

Thus, we can deduce from the analysis of the above patterns that cytotoxic drugs cause the following:

1. Qi, Blood and Yin deficiency (of Stomach, Lungs, Liver and Kidneys)
2. Stomach-Qi rebelling upwards
3. Stomach Heat
4. Blood Heat.

The treatment principles to adopt are therefore (the herbs used are indicated in brackets):

- Tonify Qi, Blood and Yin (Huang Qi *Radix Astragali membranacei*, Dang Shen *Radix Codonopsis pilosulae*, Tai Zi Shen *Radix Pseudostellariae*, Ling Zhi *Fructificatio Ganodermae lucidi*, Shan Yao *Radix Dioscoreae oppositae*, Xi Yang Shen *Radix Panacis quinquefolii*, Mai Men Dong *Tuber Ophiopogonis japonici*, Dang Gui *Radix Angelicae sinensis*, Nu Zhen Zi *Fructus Ligustri lucidi*, Huang Jing *Rhizoma Polygonati*)
- Subdue rebellious Stomach-Qi (Lu Gen *Rhizoma Phragmitis communis*, Ban Xia *Rhizoma Pinelliae ternatae*)
- Clear Stomach Heat (Lu Gen *Rhizoma Phragmitis communis*)
- Cool Blood (Mu Dan Pi *Cortex Moutan radicis*)

Analysis of Individual Herbs in Chemo-Support

<i>membranacei</i> : tonify Qi and raise immune response.-	Huang Qi <i>Radix Astragali</i>
<i>Codonopsis pilosulae</i> : tonify Qi.-	Dang Shen <i>Radix</i>
<i>Pseudostellariae</i> : tonify Stomach-Qi and Stomach Yin. -	Tai Zi Shen <i>Radix</i>
<i>Ganodermae lucidi</i> : tonify Qi and Blood and raise the immune response.-	Ling Zhi <i>Fructificatio</i>
<i>oppositae</i> : tonify Qi.-	Shan Yao <i>Radix Dioscoreae</i>
<i>quinquefolii</i> : tonify Qi and Yin.-	Xi Yang Shen <i>Radix Panacis</i>
<i>radicis</i> : cool Blood.-	Mu Dan Pi <i>Cortex Moutan</i>
<i>cocos</i> : resolve Dampness.-	Fu Ling <i>Sclerotium Poriae</i>
<i>reticulatae</i> : resolve Dampness, stop nausea.-	Chen Pi <i>Pericarpium Citri</i>

Ophiopogonis japonici: nourish Yin.-

sinensis: nourish Blood-

ternatae: resolve Phlegm, subdue rebellious Stomach-Qi, stop nausea and vomiting.-

communis: clear Stomach-Heat, stop vomiting.-

lucidi: nourish Yin.-

Polygonati: tonify Qi, nourish Yin and Jing.-

uralensis: harmonize.

Mai Men Dong *Tuber*

Dang Gui *Radix Angelicae*

Ban Xia *Rhizoma Pinelliae*

Lu Gen *Rhizoma Phragmitis*

Nu Zhen Zi *Fructus Ligustri*

Huang Jing *Rhizoma*

Gan Cao *Radix Glycyrrhizae*

Pharmacology of Chemo-Support Ingredients

I shall report only the pharmacology of the above plants that is relevant to chemotherapy, immune function, inflammation, digestion or carcinoma. Thus, for each plant, there are many other pharmacological actions not reported below. These data are not available for all of *Chemo-Support's* ingredients.

It should also be noted that such data are reported for reference only as they reflect a reductionist view of the action of herbs that is at variance with the Chinese medicine view. Some of the research studies reported present a doubly-reductionist view: firstly, they use single herbs and secondly, many of them use single constituents of a herb. By contrast, Chinese medicine uses only formulae composed of several herbs. It is a well-known fact that first of all, the action of a herb is more than the sum-total of the actions of its individual constituents and secondly, the synergistic action of a formula is more than the sum total of its individual herbs.

Furthermore, many of the studies reported are based on animal experiments which could be criticized on ethical grounds.

HUANG QI Radix Astragali membranacei

Constituents

2'4'-dihydroxy-5,6-dimethoxyisoflavone, kumatakenin, choline, betaine, polysaccharides, glucuronic acid, folic acid.

Pharmacology

1. Enhancement of immune function

The decoction given to mice increased the phagocytic activity of the reticuloendothelial system. Oral administration or nasal spray of Huang Qi offered protection against the common cold. Intraperitoneal administration of the polysaccharides from the root of *Astragalus membranaceus* antagonized the atrophy of immune tissues such as spleen, thymus and intestinal lymph nodes as well as leukopenia caused by immunosuppressant prednisolone in mice. Intraperitoneal administration of the homogeneous fraction of the polysaccharides astragalin I and II increased the weight and cell number of mouse spleen. Two months of oral treatment with the herb in subjects susceptible to common cold greatly increased the levels of SIgA and IgG in the nasal secretion.

2. Antibacterial effect

In vitro, Huang Qi was effective against *Shigella shigae*, *Bacillus anthracis*, *Streptococcus hemolyticus*, *Corynebacterium diphtheriae*, *Diplococcus pneumoniae*, *Staphylococcus aureus*.

3. Prevention of renal toxicity in chemotherapy

A double-blind trial of 49 patients undergoing chemotherapy showed that the decoction of Huang Qi *Radix Astragali membranacei* and Fu Ling *Sclerotium Poriae cocos* markedly reduced the incidence of renal toxicity. Rats with experimentally-induced glomerulonephritis, when treated with Huang Qi had significantly less proteinuria than control groups as well as milder pathological tissue changes.

4. Effect on endurance

Decoction of Huang Qi given to mice significantly increased their endurance in swimming tests.

5. Endocrine effect in patients undergoing radiotherapy

In a randomized clinical trial, the plasma hydrocortisone level in stage II carcinoma of the cervix was observed. The average level in 18 patients before and after irradiation were 8.0 and 6.1 µg/100ml, whereas the before and after levels were 9.5 and 9.1 µg/100ml in patients who received a decoction of Huang Qi *Radix Astragali membranacei* and Nu Zhen Zi *Fructus Ligustri lucidi* for two months.

6. Anti-inflammatory effect

Intravenous dose of 5 mg/Kg or oral dose of 50 mg/Kg of astramembranin I inhibited the increase in vascular permeability induced by serotonin or histamine in rats.

7. Hepatoprotective effect

Intravenous administration of 10 mg/Kg of astramembranin I induced accumulation of cAMP in rabbit plasma.

DANG SHEN *Radix Codonopsis pilosulae*

Constituents

Saponins, trace of alkaloids, carbohydrates, mucilage, resin, volatile oil, scutellarein glucoside, polysaccharides.

Dosage and Protocol

Chemo-Support works better if it is started some time before the beginning of chemotherapy and continued for about two weeks after the end. It is important to note that "during the treatment" means during the course of treatment, i.e. also in the days of break from the treatment. The dosage is as follows:

- Two weeks before start of treatment: 2 tablets twice a day
- Four days before the start of treatment: 2 tablets three times a day
- During the treatment: 3-4 tablets three times a day
- After the end of the treatment for about 2 weeks: 2 tablets three times a day

It is best to take the tablets away from meals, i.e. about 1 hours before or after a meal, swallowed with hot water. The tablets should also be taken separately from other medication, at least 1 hour away. If the patient feels very nauseous and finds it difficult to swallow the tablets, these could be crushed and powdered, immersed in a small amount of hot water and the water sipped slowly.

The dosage during treatment indicated above should be adjusted according to the severity of the side-effects and the above dosage could be reduced or increased.

If the patient is receiving both chemo- and radio-therapy and is taking both *Chemo-Support* and *Radio-Support*, the dosage of each should be reduced. Adjustments can be made according to the patient's side-effects and timing of therapies in this situation by using a higher ratio of *Chemo-Support* during the days surrounding chemotherapy or when its side-effects are heightened. Similarly, the dosage of *Radio Support* can be increased if the side-effects experienced from radiotherapy are more severe, or during the days surrounding the administration of radiotherapy.

Chemo-Support should be discontinued approximately two weeks after the end of the treatment when the condition should be reassessed and a different remedy given. By contrast, *Radio-Support* should be continued for at least 6 weeks after the end of radiotherapy.

Acupuncture Treatment of Chem-Support Side Effects

Acupuncture can be used to great effect, in conjunction with *Chemo Support* to reduce the side-effects of chemotherapy. Indeed, acupuncture can complement the use of *Chemo-Support* by tailoring the treatment to the specific side-effects suffered by the patient. The following are suggested point combinations for specific symptoms and signs.

Fatigue

Ren-12 Zhongwan, ST-36 Zusanli, SP-6 Sanyinjiao, BL-20 Pishu, BL-21 Weishu.

Nausea, vomiting

Ren-13 Shangwan, P-6 Neiguan, ST-34 Liangqiu, ST-36 Zusanli. In addition to acupuncture, the following massage technique is very effective to combat nausea and vomiting: apply a massage oil liberally to the lower legs, make a loose fist with your hands, starting from ST 36, massage downwards along the Stomach channel using the knuckle of the index fingers all the way down to the ankle and then massage upwards along the Spleen channel using your thumbs. This technique harmonizes the ascending and descending of Stomach- and Spleen-Qi, stimulating Stomach-Qi to descend and Spleen-Qi to ascend.

Alopecia

BL-17 Geshu, ST-36 Zusanli, SP-6 Sanyinjiao, LIV-8 Ququan. Add Shou Wu Pian or *Glorious Sea* to *Chemo-Support*.

Myelo-suppression

BL-17 Geshu (with direct moxa cones), BL-11 Dashu (with direct moxa cones), BL-20 Pishu, BL-23 Shenshu.

Stomatitis, mouth ulcers

ST-44 Neiting, L.I.-4 Hegu, L.I.-11 Quchi.

Cystitis

Ren-3 Zhongji, BL-63 Jinmen, BL-28 Pangguangshu, BL-32 Ciliao, SP-9 Yinlingquan.

Fever

L.I.-11 Quchi, KI-2 Rangu, Du-14 Dazhui.

Skin rash

L.I.-11 Quchi, SP-10 Xuehai.

Diarrhoea

ST-25 Tianshu, ST-37 Shangjuxu.

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