A standard treatment option for Limited Small Cell Lung Cancer

Lung cancer, as with all other cancers, arises from an abnormal growth of normal cells, which have lost their function and their regulatory mechanisms that would under normal circumstances control growth. Essential for tumour growth is maintenance of sufficient blood supply. At early stages of cancers, with a small tumour, nutrients and blood will enter the cancerous growth by diffusion. At later stages, the tumour will develop new blood vessels as a response to a growth factor from the tumour. (Patrick G., 2009).

Signs and symptoms of lung cancer depend on the size of the tumour, the location and the degree of spread outside the lungs. Symptoms connected with the primary tumour are coughing, wheezing, chest pain and dyspnoea. In cases of a larger tumour (late detection of cancer) symptoms also include airway obstruction, fever and pneumonia. Metastases can occur outside the primary tumour – these are secondary tumours that have been released from the primary tumour and are positioned in other parts of the body, travelling through the blood vessels or the lymphatic system. (Koda-Kimble A. et al, 2008). A regional spread means that the cancer has spread to the lymph nodes and elsewhere in the thorax, and the symptoms are often dysphagia, superior vena cava obstruction and plural effusion. If the secondary tumours have spread to other organs or structures, the spread is defined as distant, such as spreading to the liver or brain.

In terms of lung cancer, there are two different types. One is non-small cell lung cancer which is a group of lung cancers, the different forms being adenocarcinoma, bronchioloalveolar carcinoma, squamous cell carcinoma, large cell carcinoma, and differentiated and undifferentiated lung carcinoma. The non-small cell lung cancer is thought to develop from the foci of the dysplastic surface of the bronchial tree. (Cowell J.K., 2001). This type of lung cancer is not very likely to metastasise to other structures and parts of the body in the early stages. However, it is not very sensitive to chemotherapy but combination chemotherapy can improve survival. (Koda-Kimble M. et al, 2008). Surgery is normally used as a curative treatment in non-small cell lung cancer. The other type of cancer is defined as small cell lung cancer, the use of small cell being linked to the image of small, condensed cell in diagnostics. It is a very fast progressive form of cancer. These cells have been examined and shown to have overexpression of some neuroendocrine peptides such as gastrin-releasing peptide, insulin-like growth factor and growth-hormone releasing peptide, all serving to be factors in a positive feedback loop, making the cells unable to inhibit their own growth. (Cowell J.K., 2001). This form of cancer is very sensitive to chemotherapy, where most patients will respond to it, but there is a high rate of patients to relapse.

There are two stages in small cell lung cancer.

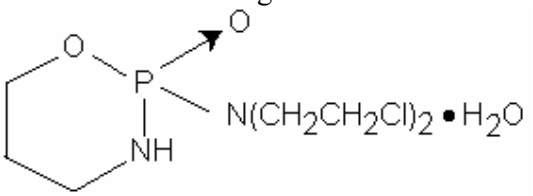
1. Limited: Cancer is confined to one hemi-thorax and only the regional lymph nodes.
2. Extended: The disease has spread to areas beyond the thorax.

The type of chemotherapy treatment is decided by the stage of cancer and an evaluation of the patient's nutritional state, the cardiac and pulmonary status respectively, and the renal and hepatic functions. (Koda-Kimble M. et al, 2008). Follow-up care must be continued after initiation of chemotherapy treatment to evaluate the toxic effects of the drug on the patient, which can include myelosuppression and renal dysfunction. It is very important to monitor any bone marrow depression. The reason for this is that cancer cells grow rapidly and will accumulate a larger amount of cytotoxic drugs compared with normal cells. However, bone

marrow cells grow very rapidly as well, so cytotoxic drugs can accumulate in normal, healthy cells giving rise to toxicity and weakening the immune system.

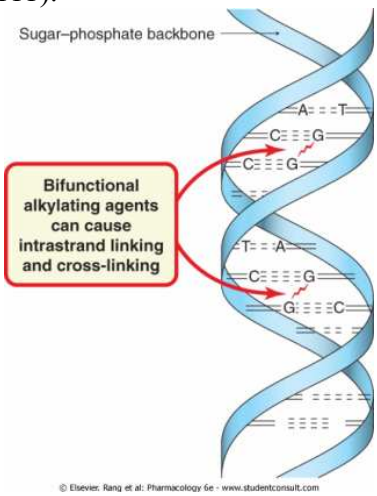
A commonly used chemotherapy combination for limited small cell lung cancer is CAV– a combination of three drugs which are cyclophosphamide - an alkylating agent , doxorubicin – an anthracycline and vincristine – a vinca alkaloid which inhibits microtubule function.

Cyclophosphamide is a synthetic anti-neoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide has the following structural formula:



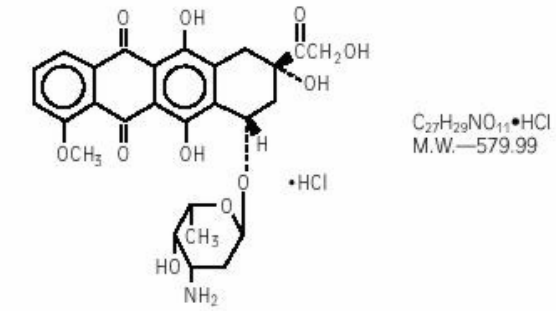
(http://www.drugs.com/pro/cyclophosphamide.html) Accessed: 30 October 2009.

Cyclophosphamide is biotransformed by the microsomal enzyme oxidation system (CYP 450) to active alkylating metabolites. The principal site of cyclophosphamide activation is the liver. The active metabolites interfere with the growth of malignant cells. (www.drugs.com). Cyclophosphamide is bifunctional, i.e. contains two alkylating groups that can form covalent bonds with particular nucleophilic substances in the cell. Cyclophosphamide is a cell cycle phase nonspecific agent. Thus cyclophosphamide prevents cell division by cross-linking DNA strands. Its principal effect occurs during DNA synthesis. Alkylation of the DNA decreases its ability to act as a template for DNA synthesis and the resulting damage triggers apoptosis (Pratt, 1995, pp.108 -111).



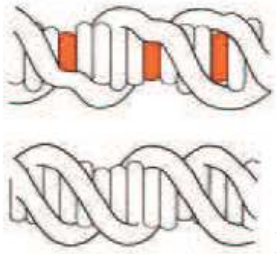
The effects of bifunctional alkylating agents on DNA. Note the cross-linking of two guanines. A, adenine; C, cytosine; G, guanine; T, thymine. (Rang and Dale, 2008, p724).

Doxorubicin is an anthracycline antibiotic isolated from cultures of *Streptomyces peucetius var. caesius*. The structural formula is as follows:



(http://www.drugs.com/pro/doxorubicin.html) Accessed: 30 October 2009.

Doxorubicin exerts its effects on cancer cells via different mechanisms. The first mechanism of action is intercalation, which involves the tight drug binding between the bases of DNA and blocking DNA synthesis and transcription. In the second mechanism of action the drug inhibits the activity of topoisomerase type II enzyme. This leads to breaks in the genomic DNA. Both of these mechanisms result in DNA disruption that ultimately can lead to the death of the cells. (Pratt, 1995, pp.155-158).

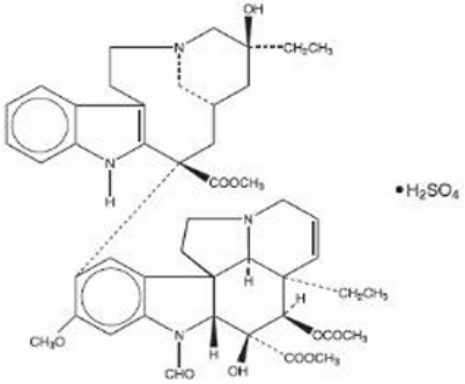


DNA intercalation. Dr. Silva E. (2009) Lecture, *Noncovalent DNA-binding anticancer drugs –topoisomerase II inhibitors.* http://blackboard.pharmacy.ac.uk

Moreover, Filyak (2008, p.67) and his research team studies suggest that doxorubicin also inhibits metastasis formation. It has been demonstrated that doxorubicin inhibits TGFβ-signaling in human lung adenocarcinoma A549 cells. The TGFβ1 (Transforming Growth Factor-β1) is a cytokine that is often up-regulated in human cancers and can promote metastasis formation.

Vincristine Sulfate is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant (*Vinca rosea Linn*). It is a microtubule inhibitor.

The structural formula is as follows: (http://www.drugs.com/pro/vincristine.html)



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Vincristine binds to tubulin in its dimeric form and disrupts the balance between microtubule polymerization and depolymerization, resulting in the net dissolution of microtubules. This results in prevention of spindle formation in dividing cells and in mitotic arrest at metaphase. (Pratt, 1995, pp.188-190).

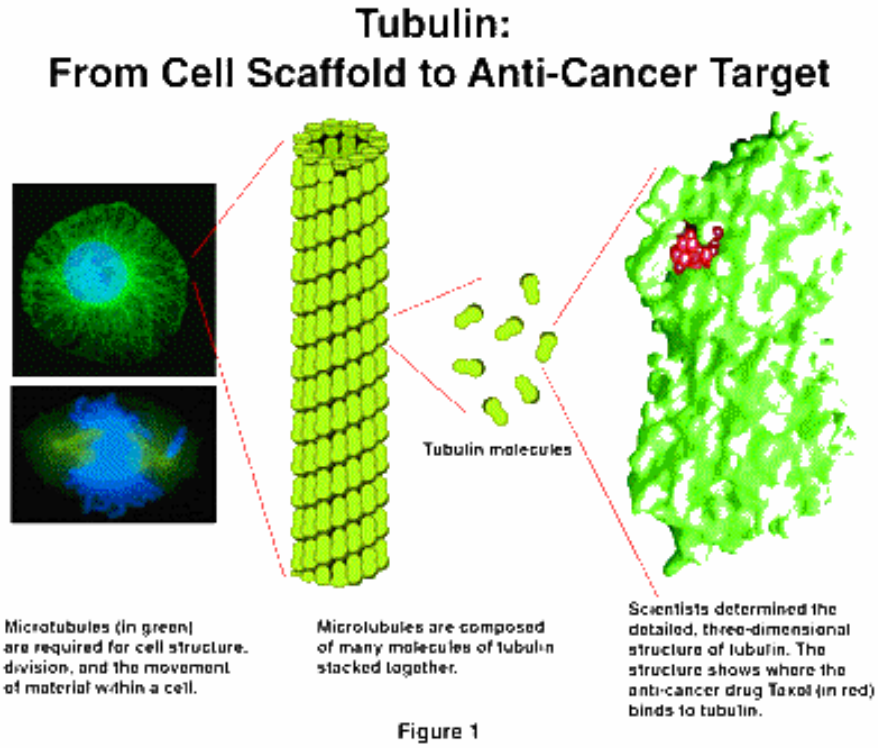

Figure 1

(http://www.nigms.nih.gov/About/Budget/Statements/February25_1999.htm)
Accessed: 30 October 2009.

Follow-up care is carried out after initiation of chemotherapy treatment to evaluate the toxic effects of the drug on the patient, and it is extremely important to be aware of the dose-limiting toxicities arising from the treatment with the anticancer drugs. Dose-limiting toxicity is the dose of a drug that produces side effects severe enough to prevent larger doses being given.

The dose limiting toxicity of cyclophosphamide is bone marrow suppression. Proliferating cells that produce mature granulocytes, erythrocytes and thrombocytes in the peripheral circulation are destroyed. As both immature cells and pre-existing mature cells are destroyed, the nadir (white blood cell count and platelet count) becomes apparent, usually 7-14 days after chemotherapy. At the same time cells in the bone marrow are maturing and are ready to be released into the peripheral blood. Within 3-4 weeks the nadir will resolve because cyclophosphamide is an alkylating agent and affects cycling and non cycling cells. When given in high doses, the stem cell population may fail to repopulate quickly enough resulting in a prolonged nadir. (Henke Yarbro C., et al page 418).
If chemotherapy is given at the time that the stem cells in the bone marrow are increasing their production this could cause permanent bone marrow damage. The timing of

chemotherapy cycles takes this process into account. For example some chemotherapy drugs are given on day 1 and day 8 of a 28-day cycle. The second dose of chemotherapy, one week after the first, is tolerated because the stem cells have not yet increased their production (they are still at the nadir). They have not increased their production because the second treatment is given before the count of the circulating blood has reached its nadir. (Chemocare.com, Hamilton S., 2005).

The dose-limiting toxicity of doxorubicin is cardiotoxicity. It is an acute or chronic process. The acute form involves transient ECG changes that occur in 10% of patients' receiving chemotherapy. This is an immediate effect and resolves quickly with serious complications. This effect is not dose related and hence not a reason to stop taking the drug. Fewer then 5% of patients develop chronic cardiotoxicity from a cumulative drug effect and hence doxorubicin should be discontinued immediately. Chronic effect occurs weeks or months after administration, involving non reversible cardiomyopathy, which is seen as a biventricular congestive heart failure (CHF). Symptoms are similar to CHF, including non productive cough, dyspnoea and pedal oedema. Doxorubicin is an anthracycline, known to cause cardiotoxicity by directly damaging the cardiac muscle cells. The mechanism of action occurs in the presence of oxygen, where the anthracyclines form a bond with iron or copper. These complexes inhibit lipid peroxidation, allowing a free oxygen radical to damage the muscles directly, this results in myocardial fibrils, mitochondrial changes and cellular destruction. As a consequence the muscle has limited contractility which increases the demand for oxygen. Cardiotoxicity has been attempted to be decreased by lowering the dose which resulted in reduction of cardiotoxicity without compromise of antitumor effects. (Henke Yarbro C., et al page 443).

The dose limiting toxicity of vincristine is peripheral neuropathy, characterized by myalgia (muscle pain) and loss of the deep tendon reflex at the ankle progressing to motor weakness, foot drop and muscle atrophy. The mechanism of action is believed to involve disruption of the microtubule in the neural tissue, which inhibits the mitotic spindle movements necessary for the mitosis phase of cellular reproduction. Vincristine doses greater than 2 mg increase the risk of neurotoxicity. (Henke Yarbro C., et al page 442).

There are many cases in which cancers that have been responding to a therapy suddenly begin to grow and cancer chemotherapy is thought to have failed. In these cases, cancer cells show insensitivity or reduced sensitivity to the effect of chemotherapy. The development of resistance to antitumor agents is considered as one of the major drawbacks encountered in cancer chemotherapy. The resistance that neoplastic cells have to cytotoxic drugs can be either primary (intrinsic) that becomes apparent when the anticancer drug is first given (*de novo* drug resistance), or developed during or after the initial treatment (acquired resistance). The latter may result from either adaptation of the cancer cells, or mutation; within all tumour populations, there is an intrinsic variation in gene expression and thus, once a tumour is exposed to chemotherapy, the cells that are less affected or unaffected by the drug are effectively selected over the sensitive cells that are killed. (Pratt W.,1994; Thurston D., 2007; Rang H., 2003). Understanding the underlying mechanisms by which tumours become resistant to cytotoxic agent(s) is the key to identifying new, more effective drugs and combination regimens. (ScienceDaily, 2005)

One of the major mechanisms cells have to detoxify cyclophosphamide that cause their death is by having high levels of glutathione (GSH) in their cytoplasm. GSH is a very reactive nucleophilic agent; it contains a sulphur group that reacts with the cytotoxic electrophilic

derivatives of alkylating agents so that they do not cause any damage to the cell. The enzyme that catalyzes the conjugation of cyclophosphamide with GSH is glutathione S-transferase and elevated expression of this enzyme makes the reaction even stronger and detoxifies the alkylating agent much quicker. Hence any tumours that have high levels of glutathione S-transferase resist the effect of cyclophosphamide a lot better. Another mechanism of resistance to cyclophosphamide is a decrease in the amount of the drug that is taken up by the cell. Tumours that are resistant to cyclophosphamide take up the drug at a slower rate than that of the drug-sensitive parent cells. However this is not usually enough to account for all the resistance alone. Rapid repair of drug-induced DNA lesions is another common mechanism of resistance to cyclophosphamide. High levels and increased expression of excision repair enzymes, which are able to cut out part of DNA that has been damaged and replace it by a new fragment, increase the chances of resistance to cyclophosphamide. (Pratt W.,1994; Thurston D., 2007; Rang H.,2003
Hamilton S., 2005)

Resistance to doxorubicin occurs through a number of different mechanisms. The main mechanism is by the decrease in the accumulation of doxorubicin with the cancer cells as a result of the increased expression of a cell-surface, ATP-dependent drug transporter protein called P-glycoprotein. The physiological role of P-glycoprotein is to protect cells against environmental toxins; P-glycoprotein acts like a pump and enhances drug efflux so that resistant cells end up with reduced intracellular drug concentrations. Multidrug resistant gene (MDR1), which is considered as one of the most important inducers of resistance to chemotherapy, codes for P-glycoprotein that can be overproduced in doxorubicin-resistant cells. Furthermore a decrease in activity of topoisomerase II can be correlated with doxorubicin resistance. Topoisomerase II winds and unwinds simultaneously both strands of DNA double helix. Doxorubicin intercalates in the DNA so that a ternary complex of drug-DNA-topoisomerase II is formed and thus, it prevents topoisomerase II form resealing the DNA fragment that was previously cleaved. Accumulation of DNA double strand breaks leads to cell death. In other words, topoisomerase II inhibition is the main mechanism of doxorubicin antitumor activity. Reduction in activity of that mechanism-critical enzyme can be a feature of drug-resistant tumours. Additionally, other cell lines have been found to have increased glutathione peroxidise activity; the biological role of glutathione peroxidase is to protect the organism from oxidative damage, but increased detoxification of reactive oxygen can result in doxorubicin resistance. (Pratt W.,1994; Thurston D., 2007; Rang H., 2003 ; Hamilton S., 2005).

Cells selected for resistance to an anthracycline are often resistant to the vinca alkaloids, as well. Resistance to vincristine usually results from decrease in the intracellular drug level due to increased drug efflux. Acquired resistance may be also correlated to overexpression of the P-glycoprotein. (Pratt W.,1994; Thurston D., 2007; Rang H., 2003 ; Hamilton S., 2005).

It is thought that once a cancer becomes resistant to one drug or group of drugs, it is more likely to become resistant to other drugs, as well. This is why it is crucial to select the best possible initial treatment for each patient. Resistance to chemotherapy is widely considered as a major obstacle to successful cancer treatment. One way to avoid the problem of resistance is the combination chemotherapy. (Thurston D., 2007; Hamilton S., 2005; National Cancer Institute (no date); Science Daily, 2005).

To conclude, small cell lung cancer has the most aggressive growth of all lung cancers, with a median survival time of only two to four months after diagnosis when untreated. It is the type

of lung cancer most responsive to chemotherapy. Combination chemotherapy regimens yield the best response rates and highest percentage of long term survivors in small cell lung cancer and a commonly used regimen as mentioned includes cyclophosphamide, doxorubicin and vincristine. Generally, the active single agent cyclophosphamide yields a 40% response rate, while vincristine yields a 35% response rate and doxorubicin yields a 30% response rate in the treatment. The regimen itself yields an 80-95% overall response rate, 50-60% complete response rate and a median survival of 12-20 months in patients with limited disease. (Edwards R., 2001). Therefore, chemotherapy prolongs survival time four-to fivefold, however, of all patients with small cell lung cancer, only 5-10% are still alive five years after diagnosis.

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