

## Principles Underpinning the Treatment of Cancer with Drugs

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### ABSTRACT

There are many approaches to the treatment of cancer including radiological, surgical, the use of pharmaceuticals and various combinations of the above. The treatment of cancer is also continually changing with the arrival of new scientific discoveries. Currently the choice of treatment and management is individualised depending on cancer/tumour type, disease staging and treatment aims, such as intent for palliation or cure.

There are various types of pharmaceuticals used in the treatment of cancer; these include chemotherapy agents and specific targeted treatments of cancer including monoclonal antibodies and tyrosine kinase inhibitors. Here we explore the rationale behind the treatment of cancer with drugs, by discussing the principles of chemotherapy and the use of targeted treatments in haematological and breast malignancies.

**Key Words:** oncology; chemotherapy

### Introduction

Cancer is one of the leading causes of death in the UK. In 2008 it was responsible for one in four deaths in England, equivalent to 128,000 people<sup>1</sup>. As a disease, cancer is difficult to treat as there are numerous types with varying biology depending on tissues involved. Cancer manifests in many ways and has different sensitivities to therapeutic agents. Given these complexities, we are only just beginning to understand the pathogenesis of cancer and how we can treat it. Currently there are a number of approaches to cancer therapy and here we will discuss the principles of treating cancer with drugs, the mainstay of which consists of cytotoxic chemotherapy agents and various targeted treatments.

### Cancer

Cancer is also known medically as a malignant neoplasm. These neoplastic cells display immortality, abnormal regulation of growth, self sufficient growth, resistance to apoptosis, angiogenesis, nearby tissue invasion and the ability to metastasis<sup>2</sup>. Each cancer is classified according to the tissue it is derived from and the associated cell type, thus making each cancer unique in causation, treatment and prognosis, adding to its complexity.

The cause of cancer is thought to be due to a combination of genetic factors and exposure to a wide range of avoidable risk factors. Risk factors for cancer are numerous, the most prominent being tobacco smoking and chewing, poor diet, exposure to UV light, radiation,

obesity, hormonal influences, infections (such as Human papilloma virus which is associated with oral cancer and cervical cancer), occupation related (exposure to asbestos causing mesothelioma) and various chemicals which we are exposed to in our environment<sup>3</sup>.

As cancer encompasses such a diverse collection of disease, a number of approaches to treatments are available. These treatments can be used individually or in combination. Surgery is commonly offered to patients, often with curative intent and occasionally combined with neoadjuvant or adjuvant chemotherapy (before/after surgery)<sup>3</sup>. Other options include radiotherapy, hormone therapy, immunotherapy and the newly evolving gene therapy<sup>3</sup>. Often these approaches depend on tumour type, patient age, life expectancy and the desired quality of life. These therapies can also be used palliatively, to ease suffering in terminal conditions.

## Principles of Chemotherapy

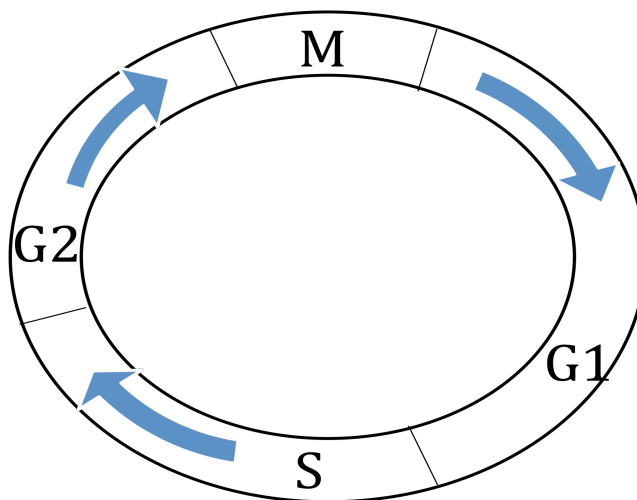
Chemotherapy is the prevention or treatment of disease by chemical substances<sup>3</sup>. The aim of chemotherapy is to selectively kill or inhibit growth of neoplastic cells whilst preserving normal cells. Chemotherapy targets cells that are rapidly dividing, and therefore affects cell multiplication and tumour growth. As a consequence, agents also target normal tissues with a high growth fraction, such as bone marrow, hair follicles, gut mucosa and skin. This causes alopecia, nausea, vomiting, diarrhoea and infections, such as neutropenic sepsis due to myelosuppression. Chemotherapy agents are discovered empirically by screening against chemical libraries. Specificity to cancer types is unknown until after testing<sup>4</sup>. There are a number of types of chemotherapy agents, which include alkylating agents, nitrosoureas, antimetabolites, anthracyclines and mitotic inhibitors. These have different modes of action, either acting at a cellular level or a cell cycle level.

Alkylating agents are activated to expose reactive alkyl groups that make covalent bonds with molecules in the cell<sup>5</sup>. These have a great affinity to bind with purines and interfere with DNA replication<sup>5</sup>. Nitrosoureas are similar to alkylating agents, they interfere with enzymes involved in DNA replication and repair<sup>6</sup>. As they are lipid soluble, they can freely pass across the blood brain barrier and are commonly used agents in the treatment of primary brain tumours.<sup>6</sup> Antimetabolites prevent DNA synthesis by inhibiting enzymes involved with the synthesis of nucleotides and amino acids. Antimetabolites are cell cycle specific and damage cells during the S phase of mitosis<sup>5</sup>. There are a number of anti-tumour antibiotics called anthracyclines. These bind to DNA and inhibit DNA and RNA synthesis<sup>7</sup>. Anthracyclines also have an effect on the enzyme Topoisomerase II, whose activity is increased in proliferating cells<sup>7</sup>. Some chemotherapy agents stop mitosis by inhibiting tubulin polymerisation<sup>8</sup>. These so called spindle poisons are plant alkaloids derived from natural products<sup>8</sup>. Table 1 summarises the different drugs and figure 1 notes the cell cycle phases where these medications may exert their effects.

**Table 1: Summary of Chemotherapy Action**

Agent Type	Method of Action	Example Drugs	Cancer Rx Examples
<b>Alkylating agents</b>	Non cell cycle specific	Chlorambucil Cyclophosphamide	Haematological
<b>Nitrosoureas</b>	Non cell cycle specific	Lomustine Carmustine	Brain Malignancies
<b>Antimetabolites</b>	Prevent S phase of mitosis	Methotrexate Cytarabine Fludarabine	Haematological Malignancies
<b>Anthracyclines</b>	Cell cycle, non specific	Doxorubicin Daunorubicin	Leukaemia, Lymphoma, Breast
<b>Spindle Poisons</b>	M phase of cell cycle	Vincristine Vinblastine	Lymphoma

**Figure 1: The Cell Cycle**



Chemotherapy agents can arrest the cell cycle at various stages. M represents the mitosis phase, G1 represents Gap 1, S represents the DNA synthesis stage and G2 is the further gap stage.

### Principles of Targeted Therapies

Targeted therapies can be defined as drugs developed against a specific target that is selected for its biological function in the cancer<sup>4</sup>. Targeted therapies are specifically designed to inhibit an abnormal target, the result of which often prevents downstream signalling, DNA synthesis or microtubule assembly. Haematological and breast cancers are leading examples of how targeted treatments are assisting in the fight against cancer. Breast

and Haematological cancers are discussed in some detail, however there are many other examples not discussed here, such as anti-androgen treatment of prostate cancer.

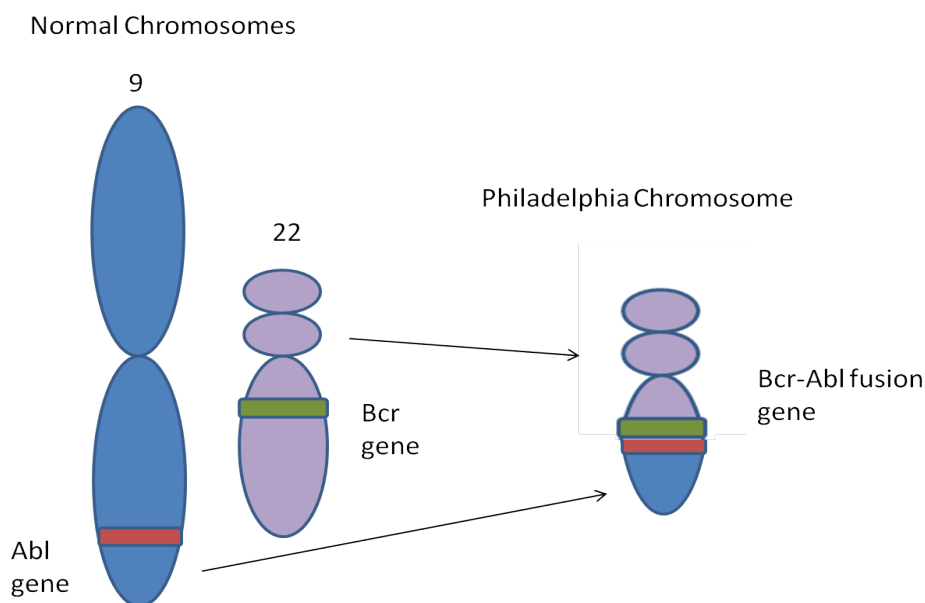
### Drug Treatment of Haematological Malignancies

Chronic Myeloid Leukaemia (CML) was one of the first malignant disorders where a genetic abnormality was discovered. The Philadelphia chromosome (PH) results from a reciprocal translocation of ABL gene on chromosome 9 and the BCR gene on 22 (Figure 2)<sup>9</sup>. The resulting effects of the BCR-ABL fusion gene are abnormal proteins with abnormal tyrosine activity<sup>9</sup>. This abnormal activity is responsible for the cells seen, with an increased cell count (abnormal proliferation) and immature cells (lack of differentiation)<sup>9</sup>.

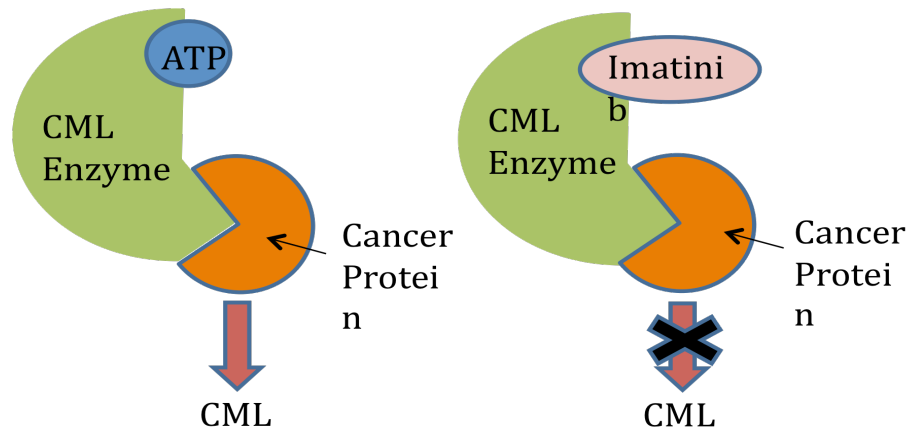
The principles for treating CML were previously based on a combination of cytotoxic (Ara-C) and immunomodulatory agents (interferon-alpha)<sup>9</sup>. The discovery of Imatinib (Gleevec), the first tyrosine kinase inhibitor, revolutionised the way that we treat CML and our approach to cancer therapies. Imatinib is an ABL specific tyrosine kinase inhibitor. This inhibits the ATP binding site in ABL tyrosine kinase which prevents the proliferative effects (Figure 3)<sup>9</sup>. Imatinib is a very effective treatment as it has been shown that 82% of patients receive a complete cytogenetic response. Studies with Imatinib alone, or Imatinib combined with another drug such as interferon, show that the best results are achieved with combinational therapies<sup>9</sup>.

Tyrosine kinase inhibitors also represent a promising approach to other non haematological neoplasms, as with gastrointestinal stromal tumours. The targeted molecular approach demonstrated in CML has also been used with other drug classes, as seen in breast cancer.

**Figure 2: Showing the translocation between Chromosome 9 and 22, resulting in the BCR-ABL fusion gene, also known as the Philadelphia Chromosome.**



**Figure 3: Method of action of Imatinib (Gleevec), showing how the drug blocks the ATP binding site, preventing tyrosine kinase function, and the production of the abnormal proteins associated with CML**



Monoclonal antibodies are widely used in haematological malignancies as a targeted treatment. Rituximab is an anti-CD20 antibody that are used in haematological conditions, such as Non Hodgkins Lymphoma and Chronic Lymphocytic Leukaemia<sup>10</sup>. CD20 is an antigen commonly found on the surface of B Cells. Rituximab is combined with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) as a highly efficacious first line treatment<sup>10</sup>. R-CHOP is a good example of a targeted therapy combined with chemotherapy and immunosuppressive agents<sup>10</sup>.

### Drug Treatment of Breast Malignancies

In the UK, breast cancer is the most common cause of solid tumour death in women<sup>11</sup>. The incidence of breast cancer increases with age, and ten years post menopause poses the highest risk<sup>11</sup>. The risk factors for breast cancer include length of reproductive life (difference between menopause and age of menarche), nulliparity (child birth is protective), weight, diet, hormone replacement therapy (exposure to exogenous oestrogen) and it is thought that 10% of breast cancers are hereditary<sup>11</sup>. The genes BRCA1 and BRAC2 are located on the long arms of chromosomes 17 and 13 and are implicated in the disease<sup>11</sup>.

Breast cancers are superficially classed as invasive or in situ. Cells that do not break through the basement membrane and remain in the terminal ducts lobular unit are non invasive<sup>12</sup>. The most common invasive breast cancers are ductal and lobular types, corresponding with the affected anatomy<sup>12</sup>.

Patients normally present after noticing a lump, or as a result of the national screening programme detecting an abnormality. For diagnosis and classification most cancers rely on histology, however some cancer classification can be done using other molecular markers. Biopsies from breast cancer tumours are tested for oestrogen receptor status (ER), Human Epidermal Growth Factor Receptor 2 (HER2) and progesterone receptor status (PR).

As prolonged oestrogen exposure is known as a risk factor for breast cancer and the identification of the ER receptor provided the first opportunity for targeted anti-oestrogen therapy<sup>13</sup>. Tamoxifen is a Selective Oestrogen Receptor Modulator (SERMS) and is a good example of hormonal therapy<sup>13</sup>. Tamoxifen blocks or down regulates the receptor, and there is resultant inhibition of the proliferative effects of estradiol at the receptor<sup>13</sup>. Tamoxifen is also prescribed to women at high risk of developing breast cancer. Other 'indirect' targeted hormone therapies are also effective. Aromatase Inhibitors block the enzyme which converts circulating androgens to oestrogens<sup>14</sup>. This is most effective in postmenopausal women as before the onset on menopause ovarian production of oestrogen is too great. Surgical options are often approached with a bilateral oophorectomy or mastectomy to remove sources of oestrogen production and sensitive tissues.

New novel therapies have provided other targeted approaches for the treatment of breast cancer. Steroid sulphatases have a role in estrogenic steroid synthesis regulation and, as breast cancers are often noted to have excess synthesis<sup>15</sup>, inhibition of this activity has been shown to be an effective treatment. The discovery of new therapies in breast cancer is important for additional or alternative therapies if resistance or intolerance is apparent<sup>15</sup>.

HER2 is a member of the epidermal growth factor receptor family receptor (EGFR) family of transmembrane tyrosine kinases which function is to regulate cell cycle<sup>16</sup>. Patients with overexpressed HER2 are more likely to have poorly differentiated tumours, with a high proliferation rate, presence of positive nodes (signifying spread) and decreased expression of oestrogen and progesterone receptors<sup>(16)</sup>. Trastuzumab is a monoclonal antibody that has a high affinity for the extracellular domain of HER2<sup>17</sup>. HER2 is commonly combined with cytotoxic agents such as taxanes, vinorelbine and platinum salts. Inhibitors of EGFR are also beneficial in the treatment of other cancers, such as advanced non small cell lung cancer<sup>18</sup>.

Micro-array profiling, which measures expression of mRNA, has given us the ability to subclassify cancer<sup>19</sup>. The information gained from this can be used to screen for those common DNA variants which have increased cancer risk, to help us determine which genes are associated with cancer survival and drug sensitivity<sup>18</sup>. This genomic medicine approach could be adopted in cancers, for example in breast cancer where they use ER, HER2, PR status coupled with genetic information to subclassify tumours. This could give an indication of prognosis and treatment plans<sup>19</sup>.

## Conclusion

Treatment of cancer can be approached in many ways: surgically, radiologically and therapeutically. The intervention used is entirely specific to cancer type and the patient. Often, combinations of approaches are used in cancer treatment for maximum effect.

Therapeutic approaches to cancer treatment usually encompass chemotherapy or targeted treatments. Both chemotherapy and targeted treatments have a positive influence on treatment survival. Conventional treatment of cancer involves numerous cytotoxic agents, either cell cycle specific or non cell cycle specific. However, more recently targeted drugs have allowed specific treatments to counter act molecular abnormalities. Targeted

treatments such as monoclonal antibodies and tyrosine kinase inhibitors have improved survival rates in some conditions. The further development of targeted treatments may revolutionise the way in which some cancers are treated. Yet despite these advances, these drugs are not always a replacement for traditional chemotherapy agents, as the greatest quality of life can often be restored through a combination of both approaches

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