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Drug Monitoring and Toxicology Laboratory

Total number of patients who received the services from Jan 2015 to December 2015 was 1291.The Summary of samples received by this laboratory during 1 year period are as follows:

Drug/Enzyme	Reference range (normal limit)	Total Samples	Results within normal limit	Results beyond normal limit	Not Detected
Carbamazepine	04-12µg/ml	84	48	21	15
Phenytoin	10-20µg/ml	218	43	112	63
Phenobarbitone	15-40µg/ml	2	-	1	1
Paracetamol	10-20µg/ml	173	8	58	107
Cholinesterase levels	4,300-11,500U/l	814	174	640	N/A
Total		**1291**	**273**	**832**	**186**

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Oral targeted therapy for cancer

Introduction

Targeted therapies block the spread or growth of cancer by interfering with specific molecules or pathways involved in the growth and progression of cancer. The target molecule may be present in normal tissue, but is overexpressed or mutated in the cancer. These drugs can be more effective than cytotoxic chemotherapy as they are specific to the cancer.[1]

Targeted therapies do not damage normal cells in the way cytotoxic chemotherapy does. Nevertheless they are still associated with some toxic adverse effects. These effects are often unique to the therapy and can be severe requiring close monitoring and clinical management. Targeted therapies can also be used in combination with chemotherapy and radiation therapy, and synergistic toxicities such as diarrhoea and skin effects can occur. Small-molecule inhibitors and monoclonal antibodies are commonly used for targeted therapy for cancer.

Small-molecule inhibitors

Mode of action

Small-molecule inhibitors are able to cross the cell plasma membrane and interfere with intracellular targets. Protein kinases play an important role in regulating cellular activity and are often found to be mutated in cancer. A number of therapies have been developed that block kinase activity and hence block cell growth. These drugs carry the suffix -nib

BCR-ABL inhibitors

Imatinib blocks the BCR-ABL protein kinase which results from a chromosomal translocation (the Philadelphia chromosome) in chronic myeloid leukaemia. Imatinib inhibits the proliferation of leukaemia cells and results in durable responses in over 80% of patients.[2] Imatinib is also active against gastrointestinal stromal tumours and certain types of acute leukaemia.

Epidermal growth factor receptor (EGFR) inhibitors

EGFR exists on the outside of cells and is activated by growth factor ligands. Once activated, intracellular tyrosine kinase activity occurs and several signal transduction cascades are initiated which lead to cell proliferation. In many cancers the EGFR activity is increased due to mutations in the receptor or tyrosine kinase protein domains. EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib, act on the EGFR tyrosine kinase domain. They are used to treat advanced non-small cell lung cancers that have the EGFR mutation.[3] Lapatinib inhibits the tyrosine kinase activity associated with EGFR and human epidermal growth factor receptor 2 (HER2).[4]

BRAF and MEK inhibitors

Other targeted drugs inhibit pathways that occur downstream of the EGFR receptor. Dabrafenib inhibits the activity of BRAF, an intracellular protein kinase of the RAF kinase family that drives cell proliferation and can be mutated in melanoma cells. Trametinib inhibits the MEK pathway and has been combined with dabrafenib in an effort to reduce resistance to dabrafenib, and to reduce some of the adverse effects associated with BRAF inhibition.[5]

Multi-targeted drugs including vascular EGR inhibitors

Sunitinib, sorafenib and pazopanib are kinase inhibitors that affect multiple pathways involved in cancer cell growth. In addition to blocking tyrosine kinase pathways they block the vascular endothelial growth factor (VEGF) protein which promotes angiogenesis. These drugs are active in a variety of cancers due to their diverse activity.

Adverse effects

Despite their selectivity, targeted therapies still have adverse effects, ranging from mild to fatal effects. Patients require constant monitoring while on therapy. It is usual for the treating haematologist or oncologist to review blood tests, liver function test, renal function test regularly. Some targeted therapies are used in combination with cytotoxic chemotherapy, For example, the combination of lapatinib and capecitabine is used in breast cancer and these patients require a regular check of their blood counts before each cycle of chemotherapy.

Common adverse effects:

- Diarrhea, Constipation
- Hypertension, Reduction in left ventricular ejection fraction, Prolongation of QT interval, Edema
- Pulmonary complications
- Bleeding, Venous thromboembolic event
- Fever, Hypothyroidism
- Papulopustular rash, Xerosis and fissures, Pruritus, Paronychia, Hand–foot syndrome and hair changes.[6]

Immunomodulatory drugs

Lenalidomide, thalidomide and pomalidomide are immunomodulatory drugs mainly used in the treatment of myeloma in combination with steroids.[7] They may also be combined with cytotoxic chemotherapy. They block several pathways that drive the progression of myeloma and have anti-angiogenic properties. There is an increased incidence of thromboembolic events in patients treated with the combination of dexamethasone and lenalidomide, thalidomide or pomalidomide, and prophylactic antithrombotic therapy is routine for these patients.[8] These drugs are associated with constipation and diarrhoea. Haematological toxicities are more common with lenalidomide, while dose-dependent peripheral neuropathy is associated with prolonged therapy with thalidomide.

All-trans retinoic acid

All-trans retinoic acid is an oral therapy used in the treatment of acute promyelocytic leukaemia,[9] usually in combination with arsenic trioxide and/or cytotoxic chemotherapy. It is a derivative of vitamin A with a distinct mode of action. All-trans retinoic acid binds to the retinoic acid gene receptor and induces the differentiation of acute promyelocytic leukaemia cells into normal mature cells. Common adverse effects include headache, fever, weakness and fatigue.

Drug interactions

It is important that an assessment is made of potential interactions between targeted therapy and other prescribed and over-the-counter medicines, complementary medicines and food. Such interactions can affect the efficacy and safety of both the targeted therapy and other therapy. The concomitant use of acid suppressive treatment (e.g. Proton pump inhibitor) should be avoided as it decreases absorption of dasatinib, erlotinib, gefitinib, lapatinib and pazopanib.[10] Food can enhance the absorption of lapatinib in an unpredictable manner and lapatinib should be taken on an empty stomach.

A number of targeted therapies are substrates for the cytochrome P450 (CYP) 3A4 enzyme.[11] Simultaneous use with other CYP3A4 inhibitors or inducers can increase or reduce concentrations of tyrosine kinase inhibitors respectively.

Drug resistance

Specific mutations often contribute directly to drug resistance, however cellular and physiological mechanisms also play a significant role. Resistance to therapy remains a significant challenge in the clinical management of cancer with targeted therapy.

Conclusion

The delivery of oral targeted therapy requires a multidisciplinary approach.[12] Treatments should only be initiated by a cancer specialist who has experience with these drugs. It is essential that health professionals managing these patients have appropriate training and skills in the use of these therapies in cancer care. They should be aware of the adverse effects and the potential for drug interactions.

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