Targeted therapies in cancer

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Abstract

Cytotoxic chemotherapy has traditionally provided the backbone of medical care for cancer. While chemotherapy remains the treatment of choice for many types of cancer, so-called 'targeted therapies' are now increasingly available within the clinic across a broad range of tumour types. Targeted therapies can inhibit specific molecular targets implicated in cancer or single oncogenic drivers, rather than affecting cell division or DNA synthesis. While often better tolerated, they can be associated with adverse events, which require specialist multidisciplinary management. Targeted therapies have changed cancer care, with tailoring to an individual patients' tumour, new approaches to dosing and disease assessment, but with an increasing burden on health economics. Rather than a disease-specific approach, these novel therapies may be of benefit in multiple cancer types. There are three main categories of targeted therapies: small molecule inhibitors, monoclonal antibodies and immunotherapies, which will be considered in this article.

Keywords Immunotherapies; monoclonal antibodies; small molecule inhibitors; targeted therapies

Introduction

Cytotoxic chemotherapy has traditionally provided the backbone of medical care for cancer. Chemotherapy targets rapidly dividing cells, including cancer cells and normal tissues thus producing a predictable toxicity profile. Since the 1990s, we have seen significant changes and advances in the management of cancer. While chemotherapy remains the treatment of choice for many types of cancer, so called 'targeted therapies' are now increasingly available within the clinic across a broad range of tumour types.

Targeted therapies, like chemotherapy, can inhibit cancer growth and the development of metastatic disease. However, their mechanism of action differs from traditional cytotoxic chemotherapy. Targeted therapies can inhibit specific molecular targets implicated in cancer or single oncogenic drivers, rather than affecting cell division or DNA synthesis. While often better tolerated, they can be associated with adverse events, which require specialist multidisciplinary management. Targeted therapies have changed cancer care, with tailoring to an individual patients' tumour, new approaches to dosing and disease assessment, and an increasing burden on health economics. Rather than a disease specific approach, these novel therapies may be of benefit in multiple cancer types.

There are three main categories of targeted therapies: small molecule inhibitors, monoclonal antibodies and immunotherapies, each of which will be discussed in turn.

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Small molecule kinase inhibitors

Kinases are important targets in cancer due to their involvement in multiple signal transduction processes, which become dysregulated and have the potential to drive cancer.[1] The ability to design highly selective small molecule inhibitors to individual kinases, which inhibit downstream signalling pathways. With an acceptable side effect profile and potential for high response rates, they provide significant opportunity for therapeutic intervention.

There are a small number of molecularly defined cancers that are driven by a single gene, which can be targeted by specific small molecule inhibitors, some of which have provided a superior clinical benefit to cancer patients over standard chemotherapy. However, despite these successes, there remains much to be learnt on how best to utilize kinase inhibitors and in what order.

Kinase activation in cancer

Oncogenic activation of protein and lipid kinases occurs as a consequence of often multiple types of genetic and epigenetic changes. This may result in increased activity of the kinase, overexpression, or the loss of negative regulation. Most frequently, genetic alterations found in cancer are somatically acquired and can result in constitutively upregulated kinase activity, and oncogene addiction.[1] An example is the *BRAF* V600E mutation, targetable in a number of different cancer types including melanoma, colorectal, papillary thyroid, lung and hairy cell leukaemia.

Genomic instability can also result in elevated kinase activity through amplification of large chromosomal regions or complex chromosomal re-arrangements such as translocation or deletion, resulting in over-expression or expression of a chimeric kinase or deregulated expression respectively.[1] The receptor tyrosine kinases EGFR, HER2/ERRB2 and CDK4 and CDK6, serine/threonine kinases are frequently over-expressed as a result of gene amplification. Kinase inhibitors targeting kinase fusions, for example, BCR-ABL1 in chronic myeloid leukaemia and ALK fusions in lung cancer, have shown remarkable clinical results and provide an ideal target because of their oncogenic dependency.

Other mechanisms of kinase activation include overexpression due to epigenetic change, activation of a kinase transcription factor, inactivating mutations of negative regulators, alternative splicing, splice mutations, overexpression of a ligand or upstream positive regulator.

These diverse and multiple processes of kinase activation present numerous important opportunities for the identification of new therapeutic targets and treatment opportunities.

Types of kinase inhibitor binding sites

Protein kinases catalyse the transfer of the terminal phosphate of ATP to substrates containing a serine, threonine or tyrosine

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residue. Most kinase inhibitors are ATP competitive and have a conserved activation loop. The classification of these molecules depends on the region of interaction in the kinase and reversibility of the inhibition (Table 1).

There are multiple examples of kinases inhibitors in the clinical setting that have produced clinically meaningful results.

Imatinib mesylate

Perhaps the most well-described example is that of the BCR-ABL1 inhibitor, imatinib mesylate, in Philadelphia chromosome positive chronic myeloid leukaemia (CML). Imatinib targets the inactive confirmation of the tyrosine kinase region of the BCR-ABL fusion protein, which is a result of the translocation and fusion of chromosome 9 region q34 that contains ABL to chromosome 22 region q11. This results in unregulated ABL tyrosine kinase. Imatinib therapy in CML has resulted in durable responses, with an 8 year survival rate of 85%.[3]

Imatinib is also used in the treatment of gastrointestinal stromal tumours (GIST), where the c-KIT protein is mutated.

Vascular endothelial growth factor

The vascular endothelial growth factor (VEGF) family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor (PIGF).[4] There are three individual receptor VEGFR-1, VEGFR-2, VEGFR-3, which are transmembrane receptors. On ligand binding, they dimerise and become activated through transphosphorylation. Many small molecule inhibitors of the VEGF family are in clinical use or trials.

Sunitinib, used in the treatment of renal cell cancer, GIST and pancreatic neuroendocrine tumours, is largely a VEGF inhibitor, although it also targets PDGFRs and other receptor tyrosine kinase inhibitors. Common side effects include impaired wound healing, hypertension, skin rash and thrombosis.

EGFR and HER2

The epidermal growth factor receptor is a transmembrane receptor, involved in multiple cell processes. On binding of ligand to the extracellular domain, receptor dimerization occurs and activation of the kinase domain and downstream signalling pathways. HER2 is overexpressed in breast cancer and drives cell proliferation, angiogenesis and invasion.[5]

Small molecule inhibitors, for example erlotinib and gefitinib, that target the EGFR ATP binding site are used for the treatment of advanced NSCLC in the presence of activating mutations within the tyrosine kinase domain of EGFR.[6] A further example is lapatinib, which inhibits both HER2 and EGFR and has been used in metastatic breast cancer in patients who have progressed following treatment with Herceptin.

Combination therapy

Combination therapy has been a method of improving not only efficacy, but also delaying the onset to resistance. Many combination therapies are now currently used within the clinic or in clinical trials. A good example if this is in melanoma, where combination therapies target the MAPK pathway at different points using a BRAF V600E inhibitor and MEK1/MEK2 inhibitor together (Figure 1). This combination has been used in clinical trials to improve outcome compared with those receiving a single agent V600E inhibitor.

Drug combinations targeting parallel kinase pathways and combined inhibition of kinases that regulate cell cycle checkpoints and phase transitions are being explored.

However, combination therapy may result in increased and unanticipated toxicity. Furthermore the questions often arise as to which drug to combine with which drug and how? The combination of kinase inhibitors with other therapies is also being explored and utilized in the clinic including chemotherapy and immunotherapy combinations. The concept behind combination therapy is the idea of directly targeting the tumour and reducing its immunosuppressive influences in order to shift the local microenvironment towards a pro-inflammatory state and enhance the activity of the immune activators.[7]

Monoclonal antibodies

Monoclonal antibodies can be used to target cancer-specific antigens found not just on the surface of cancer cells, but also within the surrounding tumour stromal and vascular cells.[8] Antibodies induce cell death through several mechanisms: antibody-dependent cytotoxicity, immune-mediated killing mechanisms and indirect effects on the stroma or vasculature. The Fc function of antibodies is particularly important, and while most antibodies are intact immunoglobulin molecules (IgG), increasingly novel constructs and the delivery of conjugated cytotoxic drugs using these. Examples of the different types of tumour-associated antigens targeted by antibodies are shown below in Table 2.[8]

Monoclonal antibodies are now used extensively within the fields of oncology and haematology and many have gained FDA and EMA approval with widespread use in the clinics. Specific examples used widely are described below.

Comparison between the different types of kinase inhibitors[2]

Type of inhibitor	Type of binding	Binding site	ATP competitive	Selectivity	Examples
Type 1	Reversible	ATP site	Yes	Low	Gefitinib Vemurafenib
Type 2	Reversible	ATP site and DFG pocket	No	High	Imatinib
Type 3	Reversible	Allosteric	No	Very high	Selumetinib
Type 4	Reversible	Allosteric	No	Very high	ON012380
Covalent	Irreversible	ATP site	No	Low	Ibrutinib Afatinib

Table 1

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