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Recent advances in the systemic therapy of cancer

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ABSTRACT The current generation of anti-cancer agents, often referred to as molecularly targeted therapies, are based on exploiting our increasing understanding of the molecular and cellular basis of cancer development and progression. This review focuses on these therapies, particularly as many of the drugs concerned have received considerable attention in the popular media.

KEYWORDS Angiogenesis, apoptosis, cell cycle regulation, cellular senescence, monoclonal antibodies, tyrosine kinase

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INTRODUCTION

One of the key challenges in the effective treatment of patients with solid tumours is the similarity between tumour and normal cells. Local therapies such as surgery or radiotherapy can be curative if the malignant cells are confined to the area treated. However, the majority of patients will require systemic therapy, usually with cytotoxic chemotherapy. Research continues into improving the efficacy of current treatment modalities; modifying surgical techniques; refining radiation delivery methods, such as the use of intensity-modulated radiation therapy; and advances in the use of chemotherapy, both with new combinations of existing drugs and the development of novel cytotoxic agents. For example, capecitabine is an orally administered fluoropyrimidine that is activated by a series of enzymatic processes to form 5-fluorouracil (5-FU) within tumour tissue, and has replaced continuous intravenous infusion of 5-FU in clinical cancer medicine. Nevertheless, the cure rate remains disappointingly low with conventional cytotoxic agents in most patients with advanced, common solid tumours.

The current generation of anti-cancer agents in development are based on exploiting our increasing understanding of the molecular and cellular basis of cancer development and progression, and are often referred to as molecularly targeted therapies. This review will focus on this approach, particularly as many of these drugs have received considerable attention recently in the popular media.

CHALLENGES OF DRUG DEVELOPMENT

Among the characteristics of individual cancer cells are aberrations in genes related to growth control, apoptosis and immortality, together with functional aberrations that support the ability of cancer cells to invade and metastasise.[1] Through our knowledge of these processes, potential targets for the development of novel cancer therapies can be identified and explored. However, the pre-clinical and early clinical evaluation of these novel therapeutic strategies presents new challenges, requiring an integrated approach from both laboratory and clinical scientists.

Pre-clinical evaluation requires demonstration of reproducible biological effects in experimental systems at concentrations of drug comparable to those clinically achievable. In addition to the conventional endpoints of toxicity and pharmacokinetics, early clinical evaluation requires demonstration of desired biological activity, particularly with those agents which are likely to have a cytostatic effect. These drugs may not have objective evidence of anti-tumour activity by classical tumour response criteria, as measured by conventional radiological techniques, in patients with advanced, bulk disease in whom these agents are invariably evaluated. Evaluation of these agents will require the identification of appropriate candidate patients (e.g. the presence of molecular target in biopsy material) and demonstration of desired biological effect, usually in tumour biopsy material or by assessment of surrogate biological endpoints.

SIGNAL TRANSDUCTION INHIBITORS

The processes of normal cell growth, proliferation, differentiation and death are controlled by signals that balance their activation and inhibition. Disruption of normal cellular signalling enables malignant cells to proliferate and/or survive when normal cells would not. The process of signal transduction typically involves ligand binding to, and activating, a specific receptor. This initiates a cascade of enzymatic and biochemical reactions, allowing proliferation signals to be transmitted from the cell surface, through the cytoplasm, to the nucleus.[2] While several strategies have been proposed to inhibit a number of biologically relevant signal transduction pathways, inhibitors of tyrosine kinases are among the most explored.

Tyrosine kinases (TK) are a family of enzymes that catalyse the phosphorylation of the phenolic moiety of tyrosine residues, and abnormal 'activation' of this group of signalling proteins has been implicated in malignant growth and progression. Common to the structure of all TKs is a substrate-binding domain, an ATP-binding domain and a catalytic or kinase domain.[3] Several strategies have been proposed to target specific signal transduction pathways as potential anti-cancer therapies,[3] including inhibiting receptor–ligand interactions, inhibiting the TK domain of receptor tyrosine kinases (RTKs), inhibiting non-receptor TKs, and antisense oligonucleodies against RTK mRNA.

The most striking example of the potential use of these approaches in clinical practice is imatinib mesylate in chronic myeloid leukaemia (CML). The Philadelphia chromosome is the result of a t(9;22) reciprocal translocation, is present in more than 90% of patients with CML and results in the juxtaposition of DNA sequences from the *BCR* and *ABL* genes. *BCR-ABL* encodes a protein, p210BCR-ABL, with dysregulated TK activity which is necessary and sufficient for leukaemogenesis. Imatinib mesylate is a potent competitive inhibitor of the TKs associated with ABL and thereby inhibits their ability to phosphorylate and activate proteins downstream. Based on a comparison with interferon alpha combined with low-dose cytarabine in newly diagnosed chronic-phase CML (n=1,106), imatinib mesylate is now the standard of care in these patients. Imatinib mesylate is also active in inhibiting other TKs, including the transmembrane receptor KIT, and consequently it has become the standard of care in patients with gastrointestinal stromal tumours (GIST) who have frequent gain-of-function mutations of KIT, with KIT activation occurring in almost all cases of GIST regardless of the mutational status of KIT.

The human epidermal growth factor receptor (HER) family consists of HER1 (also called epidermal growth factor receptor or EGFR), HER2 (also called erbB2 or HER2/neu), HER3 (also called erbB3) and HER4 (also called erbB4). Drugs designed to target EGFR and HER2 are already established in clinical practice. An example of an approach to inhibit receptor–ligand interactions of RTKs is to use monoclonal antibodies against the receptor. Trastuzumab (herceptin) is a highly purified, recombinant, DNA-derived, humanised, monoclonal antibody, which binds with high affinity and specificity to the extracellular domain of the HER2 (erbB2) receptor. Amplification of erbB2 occurs in approximately 20% of breast cancers and is associated with poor prognosis. Trastuzumab can down-regulate HER2 and angiogenic proteins, such as vascular endothelial growth factor (VEGF), and induce antibody-dependent cellular cytotoxicity. Studies have shown encouraging rates of response to single agent trastuzumab, and when combined with chemotherapy it produces higher response rates and increased survival compared to chemotherapy alone in patients with advanced breast cancer.[4] The addition of trastuzumab to standard adjuvant chemotherapy regimens for patients with HER2-positive early breast cancer can significantly improve disease-free survival.[5]

Epidermal growth factor receptor is abnormally activated in many epithelial tumours. Several mechanisms can lead to aberrant receptor activation including receptor over-expression, gene amplification, activating mutations and over-expression of receptor ligands and/or loss of their regulatory mechanisms. In addition to monoclonal antibodies directed to the extracellular domain of the receptor such as cetuximab, a second class of anti-EGFR agents is designed to target the kinase domain directly, either by competitive substrate inhibition or by competitive inhibition of the ATP-binding site. These include erlotinib (Tarceva), for the second-line treatment of advanced non-small cell lung cancer (NSCLC) and in combination with gemcitabine for advanced pancreas cancer, and gefitinib (Iressa).

The development of gefitinib highlights some of the challenges in the clinical evaluation of novel agents. In pre-clinical studies, gefitinib showed activity against a broad panel of tumour cell lines expressing EGFR, with clinical activity observed in lung and colonic cancers, including significant responses in some patients with advanced, treatment-refractory lung cancer. However, the combination of gefitinib with chemotherapy failed to demonstrate a survival advantage over chemotherapy alone in two large, randomised phase III lung cancer trials.[6] A number of possible explanations were proposed at the time to explain the lack of a survival advantage in these studies, including patient selection, trial design and a possible antagonistic interaction between gefitinib and chemotherapy.

In contrast, a placebo-controlled, randomised study of single-agent erlotinib in patients with NSCLC after first-line or second-line chemotherapy showed statistically significant and clinically relevant differences for both progression-free and overall survival. In all of these studies, there seemed to be a subset of patients with NSCLC who benefited from treatment with erlotinib or gefitinib including females, patients with bronchoalveolar carcinoma and never-smokers. These clinical observations have now been followed by the discovery of somatic mutations in the TK domain of the EGFR, with a close association between these mutations and clinical responses to these agents.

INHIBITION OF DOWNSTREAM SIGNALLING PATHWAYS

The mitogen-activated protein kinase (MAPK) pathway integrates a wide array of proliferative signals initiated by RTKs and G protein-coupled receptors with potential

downstream effector proteins including raf, MAPK-kinase and ERK. The most prominent example of a potential therapeutic against raf is sorafenib, a potent competitive inhibitor of ATP binding in the catalytic domains of C-raf and of RTKs involved in tumour progression and angiogenesis including VEGF and c-kit. In patients with hepatocellular cancer with preserved hepatic function and who were not candidates for surgery, percutaneous or loco-regional therapies, where no effective systemic therapy previously existed, sorafenib has been shown to significantly extend overall survival and is now the standard of care in this patient population.[7] Similarly in another clinically challenging situation, that of advanced renal cancer, it has been shown to significantly improve progression-free survival.

ANGIOGENESIS INHIBITORS

The inhibition of angiogenesis is considered to be one of the most promising approaches and has already led to the development of novel anti-cancer strategies. New blood vessel formation by tumours creates access to the circulation and facilitates metastases. Potentially, the inhibition of new blood vessel formation may block haematogenous dissemination of cancer cells. Endothelial cells in normal adult tissues have an extremely slow turnover rate compared with that of endothelial cells engaged in active tumour angiogenesis. Therefore, it is likely that agents that selectively block endothelial cell proliferation would be relatively non-toxic. Moreover, as endothelial cells have a low mutation rate, the chances of developing acquired drug resistance would be less. For example, bevacizumab (Avastin) is a humanised antibody that targets the receptor for VEGF, one of the most important pro-angiogenic growth factors. It can improve overall survival in combination with chemotherapy in advanced colon cancer and in non-small cell lung cancer, can improve progression-free survival in advanced breast cancer and has promising activity in renal cancer and a range of other tumour types.[8]

AGENTS IN CLINICAL DEVELOPMENT

A large number of promising putative anti-cancer agents are currently in pre-clinical or clinical development and may potentially be useful anti-cancer therapies in the near future. These include agents that target:

- Signalling pathways, including ras, raf, mek and erk kinases, c-kit, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor (FGF) receptors, insulin-like growth factor 1 (IGF-1) receptor, c-met, Src family kinases and the PI3/Akt/mTOR pathway;
- Cell cycle regulation, including cyclin-dependent kinases, agents that target mitosis (e.g. Aurora and Polo kinases) or survivin;
- Apoptotic pathways, including death ligand family members (e.g. TNF-related apoptosis-inducing ligand [TRAIL]), as well as manipulation of p53, mdm2 inhibitors and targeting bcl-2;
- Molecular chaperones (e.g. heat shock protein 90 [HSP90]) and the ubiquitin-proteosome system;
- Histone deacetylase inhibitors and inhibitors of DNA methyltransferases;
- Cellular senescence and telomerase;
- Inhibitors of DNA repair mechansims, e.g. inhibitors of Poly(ADP-Ribose) Polymerase (PARP).

In addition, there is continued development of agents altering matrix metalloproteinases (MMP) biology, differentiation agents, immunotherapy and genetic therapies. A discussion of the scientific rationale, the promises and pitfalls and the results to date of the pre-clinical and clinical evaluation of each of these approaches is beyond the scope of this current review. Nevertheless, it is likely that some of these agents will feature in medical headlines in the future.

KEY POINTS

- Research continues into modifying surgical techniques, refining radiation delivery methods and in developing novel cytotoxic chemotherapy agents.
- The current generation of anti-cancer agents in development is based on exploiting our increasing understanding of the molecular and cellular basis of cancer development and progression.
- Disruption of normal cellular signalling enables malignant cells to proliferate and/or survive when normal cells would not.
- Trastuzumab in combination with chemotherapy results in improved objective response rates and increased survival compared with chemotherapy alone in patients with advanced breast cancer.
- Erlotinib has demonstrated activity in the second-line treatment of advanced non-small cell lung cancer and in combination with gemcitabine for advanced pancreas cancer.
- Bevacizumab can improve overall survival in combination with chemotherapy in advanced colon cancer and in non-small cell lung cancer, can improve progression-free survival in advanced breast cancer and has promising activity in renal cancer and a range of other tumour types.
- Sorafenib significantly improved overall survival of patients with hepatocellular cancer with preserved hepatic function who were not candidates for surgery, percutaneous or loco-regional therapies.
- The development of biomarkers is required to identify subsets of patients who might benefit from treatment with a targeted anti-cancer agent.

CONCLUSIONS

The management of malignant disease remains one of the most challenging areas of modern medicine. It is hoped that recent advances in systemic therapy, particularly as the role of targeted agents is increasingly explored, can translate into improved cancer survival rates. However, lessons have also been learnt from the clinical experience with, for example, gefitinib. The identification of the therapeutic target and therapeutic ligand remains a critical initial step in the drug development process. However, the development of appropriate biomarkers to identify the patient population who might subsequently benefit from such a targeted agent is also highly relevant to demonstrate proof of mechanism and proof of concept in early-phase studies, to enrich the patient population as part of rational clinical trial design in later phase clinical development and to select appropriate subsets of patients for treatment with specific agents when they are licensed, thereby reducing the financial implications for healthcare providers.

REFERENCES

1 Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; 100:57–70.
2 Aaronson SA. Growth factors and cancer. *Science* 1991; 254: 1146–53.
3 Hao D, Rowinsky EK. Inhibiting signal transduction: recent advances in the development of receptor tyrosine kinase and ras inhibitors. *Cancer Invest* 2002; 20:387–404.
4 Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; 344:783–92.
5 Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; 353:1659–72.
6 Giaccone G, Herbst RS, Manegold C et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial – INTACT 1. *J Clin Oncol* 2004; 22:777–84.
7 Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *New Engl J Med* 2008; 359:378–90.
8 Midgley R, Kerr D. Bevacizumab – current status and future directions. *Ann Oncol* 2005; 16:999–1004.

FURTHER READING

- Ullrich A, Schlessinger J. Signal transduction by receptors with tyrosine kinase activity. *Cell* 1990; 61:203–12.
- Druker BJ, Talpaz M, Resta DJ et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukaemia. *N Engl J Med* 2001; 344:1031–7.
- Lynch TJ, Bell DW, Sordella R et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. *N Engl J Med* 2004; 350:2129–39.
- Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. *Nat Rev Genet* 2002; 3:415–28.
- Evans J, Chitnis MM, Talbot DC. Principles of chemotherapy and drug development. In Price P, Sikora K, Illidge T, editors. *Treatment of cancer* (5th edition). London: Arnold; 2008. p.75–111.

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