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Potential of biologically targeted therapies for breast cancer

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Abstract

Despite progress in understanding the molecular and cellular basis of cancer, translation of this information into new therapies has been a complex process. Targeted therapies, which have been used in several disease areas for decades, have only recently been utilised as an approach to treatment. There are many potential targets for therapy. Targets that are under clinical investigation include the family of epidermal growth factor receptors (EGFRs or erbB) as well as vascular endothelial growth factor (VEGF), both of which play an important role in malignant cellular growth. Currently available biological agents with proved efficacy are directed against either EGFRs, VEGF or tyrosine kinases and include trastuzumab, cetuximab, bevacizumab, gefitinib, erlotinib and imatinib. Moreover, the development of agents targeting multiple pathways has resulted in additional effective agents such as lapatinib and enzastaurin. This overview briefly evaluates the promising areas for cancer targeted therapy as well as some of the targeted agents that have already impacted or are just setting out to change treatment paradigms of various malignant disorders.

Keywords: Tyrosine kinase; ErbB; Epidermal growth factor receptor; Vascular endothelial growth factor; Trastuzumab; Bevacizumab; Enzastaurin; Cancer

1. Introduction

There have been many exciting developments in the field of biologically targeted therapies in cancer in recent years. However, the concept of biologically targeted therapy itself is not a new one, as demonstrated by the use of angiotensin converting enzyme (ACE)-inhibitors in the treatment of hypertension for over 20 years. By comparison, the developments in the field of oncology are relatively recent, as evidenced by the introduction of trastuzumab into the treatment of breast cancer.

The concept of cellular traits, or acquired capabilities of all types of human cancer was introduced in 2000 [1]. At this time, the mechanisms and characteristics of malignant cell growth were well characterized. These included self-sufficiency in growth signals, evasion from apoptosis, continuous replicative potential, angiogenesis, and stromal invasion with the development of metastases. The introduction of the *bcr/abl* tyrosine kinase inhibitor imatinib represented a hypothesis-generating change of treatment paradigm, proving the efficacy of targeted therapy in diseases that are crucially dependent on their biological behaviour upon the uninhibited function of the relevant target. Extending our knowledge of the mechanisms of malignant cell growth and of available treatments to the year 2006, based on capabilities recognized ever since, reveal targeted treatment options now available. Table 1 represents some of these options. There are many potential targets for therapy, including plasmatic and membrane-associated receptors for known or even unknown ligands, receptor tyrosine kinases, gene mutations resulting in defective regulation of apoptosis, epigenetic silencing of tumour suppressor genes, and mechanisms involved in angiogenesis.

2. Oestrogen-receptor signalling pathways

The interaction of oestrogen with its receptor (ER) leads to the inhibition of apoptosis and altered cell cycle control resulting in cellular proliferation. There are at least two molecular mechanisms that may be involved in the interaction of oestrogen with ER in the tumour cell; one is via the Ras- / Raf-, MAPK and PI3-kinase pathways, whilst the other is an interaction of epidermal growth factor (EGF) with its receptor (EGFR). The involvement of these two mechanisms might also explain the evasion from inhibition of interaction of oestrogen with ER by agents such as tamoxifen and other drugs interacting with oestrogen metabolism [2].

3. Protein kinases in cancer

Protein kinases can be modulated in several ways including the abundant availability of growth factors, overexpression

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Table 1
Selected targeted treatment options in cancer, 2006. Modified according to [1]

Acquisition	Mechanism	Treatment
Stimulation of growth	Activation of erbB oncogenes	Anti-erbB antibodies, TKI
Evasion from apoptosis I	Loss of p53, Bcl-2 expression	p53 gene therapy, Bcl-2 antisense
Evasion from apoptosis II	Induction and potentiation of (drug-induced) apoptosis	TRAIL
Evasion from apoptosis III	Activation of PI3K-Akt and MAPK pathways	Bortezomib, TKI, mTOR inhibitors
Angiogenesis	Induction of VEGF	VEGF antibodies, VEGF TKI
Tumour suppressor gene inactivation	Epigenetic mechanisms	Demethylators, deacetylactors

Table 2
Mechanisms resulting in activation of protein kinases in human cancer

Overexpression of growth factor receptors
ErbB1–4 in breast, lung, colon, pancreas, and ear, nose and throat
PDGFR in glioblastoma
IGF-IR in solid tumours
Overproduction of growth factors
TGF-α
PDGF-BB expression in glioblastoma
VEGF expression
Altered protein kinase levels and/or activities
Bcr-Abl in CML (95%), ALL (15%)
c-met, c-kit in renal carcinoma
PKC
Raf-kinase (bladder, colon, lung, breast)

ErbB, epidermal growth factor receptor; PDGRF, platelet-derived growth factor; PKC, protein kinase C; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

of growth factor receptors, and altered protein kinase levels and/or function. Examples of mechanisms resulting in activation of protein kinases in human cancer are shown in Table 2.

4. Therapeutic modulation of growth factor-mediated signalling

Although many potential targets exist, there are only a limited number of drugs that have resulted in recent changes in treatment paradigms. These include the anti-growth-factor-receptor antibodies trastuzumab and cetuximab and the VEGF ligand-directed antibody bevacizumab. The tyrosine kinase inhibitors imatinib, gefitinib and erlotinib also constitute very important developments.

The family of EGF (erbB) receptors may be used as an example of an ideal target in the development of targeted therapy directed against primarily erbB1 and erbB2. The family consists of four receptors, which differ in the availability of ligands and receptor tyrosine kinases: for erbB1 (EGFR), there is an abundance of ligands, whereas no ligand is known to date to interact with erbB2 (or HER-2/*neu*), yet the receptor possesses a functioning tyrosine kinase. In contrast, erbB3 does have a ligand, but no functioning tyrosine kinase, thus making direct signal transduction via this receptor impossible, although hypotheses have been generated on the possible relevance of cross-linking receptors that might make use of each other's available compound.

Interaction of antibodies directed against erbB1 or erbB2 receptors results in well known effector mechanisms. Thus, the anti-HER-2/*neu* antibody trastuzumab leads to receptor (erbB2) down regulation, inhibition of heterodimer formation, arrest of cell cycle in G1, and induction of apoptosis. Apart from influencing these mechanisms, trastuzumab also induces immune-mediated processes such as antibody- or complement-dependent cellular cytotoxicity. The binding site of trastuzumab on the HER-2/*neu* epitope has been identified, and mimotope matching onto loop 3 has recently confirmed its location [3,4]. The clinical evidence of the efficacy of trastuzumab is overwhelming, such that in the adjuvant setting, trastuzumab significantly reduces the rate of relapse (>50%) and ameliorates overall survival in HER-2/*neu* overexpressing early breast cancer [5,6]. These data on the use of trastuzumab in the adjuvant setting were built upon previous results obtained with the drug in metastatic disease where a clinically highly relevant and significant prolongation of progression-free and overall survival was demonstrated [7].

The assessment of efficacy of targeted therapy based on the observations obtained with targeted treatment directed against HER-2/*neu* in breast cancer and, even more so, with inhibition of *bcr/abl* tyrosine kinase with imatinib in chronic myelogenous leukaemia, shows the importance of target selection. In order to be effective, the target selected for directed treatment has to be present and has to play a decisive role in tumour cell proliferation, tumour growth or metastatic spread. The presence and role of the target in a specific malignancy need to be ascertained in preclinical and early clinical investigations.

5. Mechanism of action of anti-EGFR monoclonal antibodies

The consequences of EGFR signalling via the erbB1 receptor include an activation of both the Ras/Raf and MAPK

pathways on the one hand, and the PI3K/Akt pathways on the other, leading to an intracellular signalling cascade and activation of all the processes required for tumour growth, including tumour cell survival, proliferation, metastasis and induction of angiogenesis. Cetuximab is a monoclonal antibody known to bind to EGFR. The binding of cetuximab to EGFR results in the blockade of downstream signalling and inhibition of the above cellular processes. Mimotope technology has identified the binding site of cetuximab on EGFR that leads to competitive functional inhibition of cetuximab, thereby demonstrating its specificity [8]. The impact of anti-EGFR therapy is demonstrated by the efficacy of treatment directed against this very target in chemotherapy (irinotecan)-refractory colon cancer. A series of clinical trials are under way that test anti-EGFR treatment in various indications including front-line therapy in colorectal cancer, neoadjuvant therapy in nonresectable liver metastases, and adjuvant therapy in colorectal cancer and non-small cell lung cancer.

6. Role of tyrosine kinase inhibitors

The opportunity offered by the inhibition of tyrosine kinase lies in its targeted approach, the potentially easy barrier crossing (e.g. of the blood-brain barrier) due to the small size of the molecules, and its applicability as an oral medication. The introduction of gefitinib as the first tyrosine kinase inhibitor of erbB1 has improved our understanding both of its efficacy in EGFR mutations and in treating non-small cell lung cancer (NSCLC). Another agent from this group of targeted drugs is erlotinib, which has demonstrated activity in delaying progression of NSCLC following chemotherapy [9]. When compared with placebo, erlotinib significantly prolongs progression-free and overall survival after first- or second-line chemotherapy for NSCLC. However, EGFR (erbB1) tyrosine kinase inhibitors plus platinum-based therapy have not shown an advantage over platinum-based doublets in any controlled trial performed in unselected patients with NSCLC. These findings suggest that the selection of patients may not have been appropriate in some studies and probably demonstrates the necessity to optimize target identification in better selected and well characterized patient populations with well characterized tumours. Additional ongoing clinical trials addressing this question are using a series of drugs including new anti-EGFR antibodies and tyrosine kinase inhibitors. Currently, the most important of these drugs is lapatinib, which is a tyrosine kinase inhibitor of both erbB1 and erbB2. Lapatinib has demonstrated significant activity in metastatic breast cancer patients extensively pretreated with trastuzumab [10]. In a randomized, phase III trial, time to disease progression was significantly longer in patients receiving lapatinib plus capecitabine than capecitabine alone [10]. This encouraging result supports the continued development of lapatinib as targeted therapy for patients with HER-2/*neu* overexpressing breast cancer.

7. Vascular endothelial growth factor

Another important consideration in the development of biologically targeted therapies is vascular endothelial growth factor (VEGF), which is a key mediator of angiogenesis. Potential therapies include VEGF inhibition by the antibody bevacizumab, as well as upstream activators of VEGF synthesis or downstream signalling pathways including the activation of protein kinase C-β (PKC-β). The efficacy of VEGF-directed treatment has been demonstrated by the use of bevacizumab in patients with metastatic colorectal cancer [11]. When added to an irinotecan-containing chemotherapy regimen, bevacizumab significantly prolonged progression-free and overall survival compared with chemotherapy alone [11]. In advanced breast cancer patients, the use of bevacizumab in combination with paclitaxel has led to significant prolongation of progression-free survival and a significant increase in response rate, compared with paclitaxel alone [12]. Finally, bevacizumab has also significantly influenced progression-free and overall survival in NSCLC [13].

A review of the potential mechanisms for the efficacy of targeted therapy reveals the possibility of inhibition of cell growth and proliferation by the inhibition of multiple signalling pathways [14]. The development of drugs targeting multiple pathways is now a reality and has resulted in the development of enzastaurin, an orally administered selective inhibitor of PKC-β and the PI3K/Akt signalling pathway [15,16]. Enzastaurin has shown anti-angiogenic activity in pre-clinical models and anti-tumour efficacy in colon cancer and glioblastoma xenografts. It induces apoptosis of human tumour cells and inhibits cellular proliferation. Clinical trials in various indications are under way to test for the validity of this interesting approach.

8. Conclusion

In conclusion, this review has highlighted the great potential and the diversity of targeted therapies. A number of challenges remain and include not only the optimal choice of the target(s) in certain malignant diseases and the optimal way to influence them by appropriate treatment(s) but also the definition of valuable surrogate endpoints that can be used instead of the classical clinical evaluations of treatment response.

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