Cancer Treatment Reviews (2008) **34**, 37–48

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ANTI TUMOUR TREATMENT

New developments in multitargeted therapy for patients with solid tumours

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Received 12 September 2007; accepted 13 September 2007

KEYWORDS
Dasatinib;
Imatinib;
Multitargeted therapy;
Solid tumours;
Sorafenib;
Sunitinib

Summary Molecularly targeted anticancer therapies are now available that have been rationally designed to interact with specific proteins associated with tumour development or progression. The main purpose of this article is to review the rationale and phase II/III clinical data for approved and emerging multitargeted agents used in the treatment of solid tumours. Imatinib, sunitinib, sorafenib, and dasatinib have all produced advances in the treatment of the indications for which they are licensed and show promising activity in other tumour types. Newer multitargeted agents in development appear, from preliminary phase I and II data, to be active in a broad range of tumour types, although the clinical relevance of this activity is as yet unproven. The challenge for the future is to ensure that the potential of multitargeted agents is maximised by selecting the patient populations most likely to derive clinical benefit, by optimising the dose schedules used, and by investigating multitargeted therapies combined with other agents of the same type or with conventional chemotherapy and/or other treatment modalities.

Introduction

Non-specific cytotoxic chemotherapeutic agents generally fail to exploit unique features of malignant compared with non-malignant cells or distinct characteristics of individual tumour types. In contrast, molecularly targeted therapies have been rationally designed to interact with particular proteins associated with tumour development or progression. Many of these agents are inhibitors of receptor tyrosine kinases (RTKs) whose expression and activity is associated with one or more types of cancer (reviewed in reference[1]). An abnormal, constitutively activated BCR-ABL tyrosine kinase was found to be the pathologic cause of more than 90% of cases of chronic myelogenous leukaemia and thus provided a unique therapeutic target for the RTK inhibitor imatinib mesylate. Targeting solid tumours is a more challenging proposition because a single RTK

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0305-7372/$ - see front matter
doi:10.1016/j.ctrv.2007.09.003

abnormality is rarely, if ever, the only pathologic cause of malignancy. KIT and platelet-derived growth factor receptor (PDGFR) provide logical targets in gastrointestinal stromal tumour (GIST), while the human epidermal growth factor receptor 2 (HER2), overexpressed in 20–25% of patients with breast cancer, is also a validated target for the monoclonal antibody trastuzumab and the dual HER1 (EGFR)/HER2 RTK inhibitor lapatinib. Other inhibitors of the EGFR RTK (i.e., erlotinib and gefitinib) and a monoclonal antibody to the extracellular domain of EGFR (cetuximab) have demonstrated clinical activity in advanced non-small-cell lung cancer (NSCLC), advanced head and neck squamous cell carcinoma (HNSCC), and metastatic colorectal cancer (CRC), respectively. The vascular endothelial growth factor (VEGF) pathway plays an important role in tumour angiogenesis, which is essential for the continued proliferation and metastasis of all solid tumours, and therefore presents an attractive target for inhibition.[2] Bevacizumab is a monoclonal antibody directed against VEGF and has demonstrated activity in metastatic CRC, advanced NSCLC, and metastatic breast cancer (MBC). RTK inhibitors targeting one or more forms of VEGF receptors (VEGFRs) are also promising and discussed further in this review.

Increasingly, however, preclinical and clinical data suggest that monotherapy with single-targeted agents such as trastuzumab, erlotinib, gefitinib, cetuximab, and bevacizumab, may produce suboptimal results because multiple signalling pathways are operative in solid tumours. Thus, more than one oncogenic or angiogenic target may need to be inhibited to improve treatment outcomes. This may involve combining targeted therapies with or without traditional chemotherapeutic agents and/or using agents directed at more than one target. These 'multitargeted' therapies have the benefit of minimising the number of agents patients would be required to take. Multitargeted therapies may be combined with single-targeted agents and/or traditional chemotherapy to maximise benefit.

Several multitargeted therapies, including imatinib mesylate, sunitinib malate, sorafenib tosylate, and dasatinib, are now indicated for the treatment of various haematologic malignancies and solid tumours including GIST and advanced renal cell carcinoma (RCC). These agents, along with an increasing number of investigational products (Table 1 and Figs. 1 and 2), are also in development for the treatment of a broad range of other solid tumours.

Table 1 Principal molecular targets of multitargeted anticancer agents and phase of clinical development, with indications approved (if any)

Drug	Company	Phase of clinical development	Indications approved	Principal molecular targets									
				VEGFR	PDGFR	KIT	FGFR	FLT3	EGFR	RET	RAF	SRC	BCR-ABL
Imatinib (STI571)	Novartis	III	ALL, CML, GIST		X	X							X
Sunitinib (SU11248)	Pfizer	III	GIST, RCC	X	X	X		X		X			
Sorafenib (BAY43-9006)	Bayer	III	RCC	X	X	X				X	X		
Dasatinib (BMS-354825)	Bristol–Myers Squibb	III (CML) I (solid tumours)	ALL, CML		X	X						X	X
Vatalanib (PTK787/ ZK 222584)	Novartis/Bayer Schering	III		X	X	X							
ZD6474	AstraZeneca	II		X					X	X			
Axitinib (AG-013736)	Pfizer	II		X	X	X							
GW786034	GlaxoSmith-Kline	II		X	X	X							
AZD2171	AstraZeneca	II		X	X	X							
AEE788[a]	Novartis	I		X					X				
BIBF 1120	Boehringer	I		X	X		X					X	
BMS-582664	Bristol-Myers	I		X			X						
AMG 706	Amgen	I		X	X	X				X			
CHIR-258	Novartis	I		X	X	X	X	X					
BAY 57-9352	Bayer	I		X	X	X							
XL999	Exelixis	I		X	X	X	X	X				X	
XL820	Exelixis	I		X	X	X							

ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; GIST, gastrointestinal stromal tumour; RCC, renal cell carcinoma.

[a] AEE788 also inhibits HER2.