Introduction to ‘A multitargeted approach: clinical advances in the treatment of solid tumours’

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Although single-target agents have been shown to improve patient outcomes in certain tumour types, drug resistance often occurs due to salvage pathways that compensate for the inhibited signalling pathway. Simultaneous inhibition of individual target receptors along multiple pathways has been shown to have additive inhibitory effects on tumour growth and vasculature, and data supporting the efficacy of strategies incorporating multitargeted agents in the treatment of several tumour types have already begun to emerge in the clinical setting. This supplement provides an overview of presentations from a satellite symposium that took place at the European Society of Medical Oncology congress on 29 September 2006, entitled ‘A Multitargeted Approach: Clinical Advances in the Treatment of Solid Tumours’, which discusses the most recent data on multitargeted agents with a focus on sunitinib malate (Sutent®, Pfizer Inc.).

Key words: sunitinib, TKI, angiogenesis, VEGF, multitargeted

Introduction

Traditional paradigms for treating solid and non-solid tumours involve the use of cytotoxic chemotherapeutic agents, which disrupt cell division in a non-cell-specific manner and thus do not target the individual features of tumour cells exclusively. Since these drugs are unable to distinguish between malignant and non-malignant cells, their use is limited by significant side effects and safety concerns. Therefore, there is an urgent need to rationally design novel, molecularly targeted anticancer therapies, which are more selective, ideally less toxic and ultimately more effective than traditional treatments.

Emerging understanding of the molecular processes underlying tumour growth has identified an array of molecules fundamental to both tumorigenesis and angiogenesis. In particular, several members of the split-kinase domain superfamily of receptor tyrosine kinases (RTKs) such as platelet-derived growth factor receptors (PDGFRs), vascular endothelial growth factor receptors (VEGFRs) and stem cell factor receptor (KIT) are expressed on either epithelial cells, stromal cells or both in a variety of cancers, and are integral to the signalling cascades that directly and indirectly regulate tumour development and progression and angiogenesis [1–3]. Each of these receptor families may contain several related RTKs and complementary ligands with overlapping biologic functions. Therefore, a multitargeted approach where several of these growth factor pathways are selectively and simultaneously blocked at the RTK level represents an attractive therapeutic strategy.

This supplement to Annals of Oncology is based on the proceedings of the symposium entitled ‘A Multitargeted Approach: Clinical Advances in the Treatment of Solid Tumours’, held during the 31st congress of the European Society of Medical Oncology in Istanbul, Turkey, on 29 September 2006. The supplement primarily focuses on data for the oral multitargeted RTK inhibitor sunitinib (Sutent®, Pfizer Inc.). In January 2006, sunitinib was approved by the US Food and Drug Administration (FDA) for treating gastrointestinal stromal tumor (GIST) after disease progression or intolerance to imatinib therapy and for advanced renal cell carcinoma (RCC). Additionally, the European Agency for the Evaluation of Medicinal Products granted similar approval of sunitinib for GIST (July 2006) and approval for first-line treatment of advanced and/or metastatic RCC in January 2007.

The first article, by Dr Christensen, summarizes the preclinical data for sunitinib, focusing on the mechanism of action and evidence of the agent’s antitumour and antiangiogenic activity in tumour models. Next, Drs DePrimo and Bello review the pharmacokinetics and pharmacodynamics of sunitinib and explore potential biomarkers of its pharmacological activity. In the third article, Drs Judson and Demetri examine the efficacy and tolerability of sunitinib in patients with imatinib-resistant GIST. The results of the pivotal randomized phase III placebo-controlled study show that sunitinib provides clinical benefits including significant improvements in time to progression and survival. This is combined with an acceptable safety profile [4]. In their article, Dr Oudard et al. review the effects of sunitinib in metastatic...
RCC. In phase II trials in patients with cytokine-refractory RCC, the use of sunitinib in the second-line setting substantially prolonged disease progression [5, 6]. Similar benefits were also observed with first-line sunitinib [7]. In a phase III comparator trial, sunitinib demonstrated significant improvements in progression-free survival and objective response rate compared with interferon-alfa. These results suggest that sunitinib should be considered as the new reference standard for the first-line treatment of patients with metastatic RCC.

Finally, the supplement concludes with a discussion by Dr Scagliotti on the role of multitargeted tyrosine kinase inhibitors in non-small–cell lung cancer. Several agents including sunitinib have demonstrated promising clinical effects in preliminary studies when used as monotherapy for patients with advanced disease, and are currently being investigated in a number of phase II/III combination trials in first- and second-line therapy [8–11].

The articles provide a comprehensive overview of the role of multitargeted therapies in managing solid tumours. Incorporating these agents into routine clinical practice will provide important choices for effective disease management.

disclosures

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