Summary
Antimetabolites
Kenneth W. Wyman, Igor Puzanov and Kenneth R. Hande

Antimetabolites are anti-neoplastic drugs similar in structure to the essential molecules needed for DNA synthesis (folic acid, pyrimidines and purines). Antimetabolites trigger apoptosis by interfering with some essential step in DNA synthesis. This chapter reviews currently used antimetabolite antineoplastic drugs including their mechanism of action, cellular and clinical pharmacology, and their toxicity.

Key words: Antimetabolites, DNA, purine analogs, anti-folates, pyrimidine analogs, methotrexate, 5-flouorouracil, cytarabine, mercaptopurine, azathioprine, cladribine, fludarabine, gemcitabine, hydroxyurea.

Klaus Mross, Ulrich Massing and Felix Kratz
DNA-intercalators – the anthracyclines

(No summary and key words available)

Summary
Topoisomerase inhibitors
Hans Gelderblom and Alex Sparreboom

DNA topoisomerase inhibitors, known for their broad antitumour activity, represent one of the most widely used groups of anticancer agents. In spite of the early discovery and long-standing clinical use, the mechanism of action of these agents was not recognized until the 1980's. Currently agents available for clinical use include the topoisomerase I inhibitors of the camptothecin class (topotecan and irinotecan) and the topoisomerase II inhibitors in the class of epipodophyllotoxins (etoposide and teniposide). Many new formulations and structurally-related agents are currently undergoing clinical development. This chapter highlights the most important aspects of the past, current and future development of topoisomerase I and II inhibitors, and provides an overview of pharmacology and clinical data, with a focus on recent developments.

Key words: topoisomerase I, topoisomerase II, topoisomerase inhibitors, camptothecins, pharmacology, topotecan, irinotecan, CPT-11, etoposide, teniposide, epipodophyllotoxins

Summary
Manon T. Huizing
Tubulin interacting agents

Tubulin interacting agents are an important group of drugs in the treatment of several kinds of haematological and solid tumors. Taxanes and vinca alkaloids are the two major classes of these drugs. Microtubule dynamics are extremely important for cell division, cell shape, cellular motility and attachment. Vinca alkaloids depolymerise microtubules while taxanes shift the microtubule equilibrium toward polymerisation, inducing stable microtubules that interfere with

cell division. Both classes of drugs are extensively metabolised by the liver and are prone to the development of multi-drug resistance. The most important dose limiting toxicity is disabling neurotoxicity. Novel agents are under evaluation to circumvent multidrug resistance.

Key words: tubuline interacting agents, microtubules, taxanes, paclitaxel, docetaxel, vinca alkaloids, vincristine, vinblastine, vindesine, vinorelbine, vinflunine, Cremophor EL, epothilones, small peptides, new developments

Summary
Alfonsus J.M. van den Eertwegh
Vaccination therapies in solid tumors

The goal of cancer vaccines is to induce a specific immune response against antigens expressed by the tumor cells, which eventually should result in the elimination of these malignant cells by the immune system. Various vaccination strategies have been investigated using peptides, heat shock proteins, autologous/allogeneic tumor cells, dendritic cells and viral vectors. Most studies have been performed in patients with metastatic disease, showing in a low percentage of patients clinical tumor responses. The fact that in the majority of the studies only in the minority of patients tumor specific immune responses were detected, indicate that the used immunization protocols are not yet optimal and most likely not tested in the right stage of disease. Nevertheless, great progress have been made in the field of cancer vaccines and it is expected that they will become soon one of the new modalities in the treatment of cancer. In this review the most appealing vaccination studies are discussed and the very promising results of the application of monoclonal antibodies against CTLA-4 or T regulatory cells, to enhance the efficacy of vaccines in the treatment of cancer, will be addressed.

Key words: vaccination, cancer, peptides, active specific immunotherapy, dendritic cells, heat shock proteins, cancer, anti-CTLA-4, T regulatory cells, genetherapy

Summary
Carolien H. Smorenburg and Alex Sparreboom
Oral anticancer agents

In oncology, most anticancer agents have a narrow therapeutic index and are delivered by intravenous injection. Oral chemotherapy may be a valuable alternative for reasons of patient convenience and economics. Although data confirm patient's preference for oral chemotherapy, only few studies investigated actual patient compliance. Bioavailibility indicates the fraction of a given oral drug that reaches the systemic circulation. A high variability in bioavailability and in inter- and intrapatient variability in drug exposure may limit clinical use of oral agents. Bioavailability may be hampered by mechanical barriers, intestinal drug transporters (P-glycoprotein, breast cancer-resistance protein BCRP), intestinal enzymes (cytochrome P-450 3A4, dihydropyrimidine dehydrogenase, carboxylesterase), concomitant medication, food and certain formulation vehicles of the drug. In the development of oral anticancer agents, pharmacokinetic and pharmacodynamic aspects of both oral formulations of existing cytotoxic agents as well as new targeted molecules are investigated, together with research on optimal dose scheduling and food interaction.

Key words: metronomic scheduling, preference, compliance, pharmacology, bioavailability, mechanical barrier, intestinal drug transporter, P-glycoprotein, intestinal enzyme, concomitant medication, food, formulation vehicle

Summary
Bart C. Kuenen
Anti-angiogenesis agents

Inhibition of angiogenesis is an emerging new strategy in the treatment of cancer. Sustained angiogenesis is one of the hallmarks of cancer after tumors have made the angiogenic switch. The complex process of the formation of new blood vessel is redundantly regulated by many different factors, which are normally in balance. Vascular endothelial growth factor (VEGF), up regulated in many tumors, is seen as the most pivotal player and therefore several strategies of interfering with the VEGF/VEGF-receptor pathway have been developed. Bevacizumab, a monoclonal antibody directed to VEGF, and small synthetic molecules which block the intracellular tyrosine kinase domain of the VEGFR are the most important ones. First clinical experience with these compounds as well as other strategies of modulating angiogenesis, such as the administration of endogenous anti-angiogenic proteins, will be discussed in the chapter anti-angiogenic agents.

Key words: angiogenesis, vascular endothelial growth factor (VEGF), VEGF-receptor, fibroblast growth factor (FGF), platelet derived growth factor (PDGF), family of receptor tyrosine kinases, monoclonal antibody, bevacizumab, tyrosine kinase inhibitors, endogenous anti-angiogenic proteins, endostatin, angiostatin

Summary
Ferry A.L.M. Eskens
Signal transduction inhibitors

Major advances in elucidatin the process of cellular signal transduction have taken place in the last twenty years. This process plays an important role in the development and growth of human cancer. Specific anti-receptor antibodies and receptor tyrosine kinase inhibitors have been developed. Clinical studies have shown their role in anticancer treatment. The design of clinical studies involving inhibitors of signal transduction has to be adapted regarding novel mechanisms of action of these agents and the anticipated clinical outcome.

Key words: signal transduction, receptor antibodies, tyrosine kinase inhibitors, study design

Rosalba Torrisi, Alessandra Balduzzi and Aron Goldhirsch
Endocrine therapy of breast cancer

(No summary and key words available)

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