Symposia

979

OVERVIEW OF CAMPTOTHECINS

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The Camptotethecins, synthetic and semi-synthetic plant alkaloid derivatives, are specific inhibitors of Topoisomerase I. They open a promising chapter in cancer chemotherapy.

These nuclear enzymes are rooted in the bihelical geometry of DNA. They catalyze relaxation of torsionally strained supercoiled DNA in producing a transient single strain break. At the target level, camptothecin analogues specifically inhibit the break-rejoining reactions of DNA topoisomerase I.

Approximately ten drugs of this class are presently investigated, but, only four are in the clinical development phases. The choice of the optimal dose schedule recommended for phase II is a common problem of these camptothecins. Phase II studies have been initiated for 9-AC. Topotecan and irinotecan are the most widely tested in Europe.

The most interesting activity of Topotecan seems to be reported in ovarian cancer and SCLC.

Irinotecan is the only one already commercialized (in Japan: SCLC, NSCLC, cervical ovarian cancer). A major European trial (n = 213) of Irinotecan in colorectal cancer showed a RR of 20.5% in the evaluable patients. Similar results were obtained in chemotherapy naive and pretreated patients. Other Japanese, American and European studies have confirmed this original activity in colorectal cancer and have shown promising results particularly in lung, cervical and pancreatic cancers.

In conclusion, Irinotecan is the only camptothecin derivative having shown significant clinical efficacy in a large spectrum of tumours particularly in patients with colorectal cancer.

980

NEW DRUGS IN THE TREATMENT OF MALIGNANT LYMPHOMAS

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The development of new drugs has been greatly hampered in the field of lymphomas by many methodological problems, mainly related to the heavy pre-treatment of many patients. These methodological problems will be discussed.

During the last years, however, a few interesting new compounds have emerged. The most exciting ones belong to the family of the purine-analogues, among them Fludarabine and 2-CdA (2-Chlorodeoxyadenosine) have been widely tested in many phase II trials. In selected series the response rate has approached 75–80% depending on the selection of the patients. Currently, phase II trials in previously untreated patients as well as randomized phase III trials are ongoing. Further developments in this area are represented by immunotoxins, radiolabelled monoclonal antibodies and tumour vaccines. Therapeutic possibilities as well as still existing methodological weaknesses of these approaches will be discussed.

981

THE DEVELOPMENT OF NEW PLATINUM COMPLEXES: ORAL DELIVERY AND NON-CROSS RESISTANCE

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Mixed ammine/amine platinum(IV) dicarboxylates are orally active and show *in vitro* efficacy against human tumour cell lines with acquired platinum resistance, partly by overcoming reduced uptake. The search for truly non-cross resistant platinum complexes continues. Bis-acetato-ammine-dichlorocyclohexylamine platinum(IV), known as JM216, was developed for oral use based on its good oral bioavailability, low emetogenicity, lack of nephro- or neurotoxicity, and similar antitumour spectrum to carboplatin. 2 phase I trials were performed using a single dose PO q 3w, MTD not reached owing to saturable absorption, and daily × 5 PO q 3w. 31 patients were treated over the range 30 to 140 mg/m^2/day, which was the MTD due to myelosuppression, other side effects being easily manageable. Evidence of antitumour activity was seen in patients with ovarian cancer, NSCLC and mesothelioma. Pharmacokinetics studies of free (ultrafiltrable) and total Pt showed a linear relationship between dose and both Pt AUC and C_{max}, the terminal half-life of ultrafiltrable Pt, corresponding to active metabolites, was 7.45 ± 4 h. A dose of 100 mg/m^2/day × 5 is recommended for phase II study in previously treated patients and 120 mg/m^2/day × 5 in non-previously treated patients. Phase II trials are now underway in SCLC, ovarian cancer and NSCLC.

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982

THE TAXOIDS A NEW GROUP OF ACTIVE COMPOUNDS AGAINST MANY CANCER TYPES

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The mitotic spindle poisons which stabilize microtubules and inhibit their depolymerization to free tubulin Paclitaxel (Taxol®) (P) and Docetaxel (Taxotere®) (D) were discovered in 1971 respectively 1986. Development was in the beginning impeded by difficulties in obtaining drug supply. They are now dissolved in resp. Cremophor-EL and polysorbate 80. The drugs have a different half life and must be given with prophylaxis to prevent allergic reactions. Hitherto no randomized trials comparing the two drugs have been performed. Most data are derived from phase II studies as single agents and in combination (P > D). Both drugs are active in ovarian cancer and breast cancer. D seems a little bit more active then P in lung cancer (small cell and non small cell). They are both active against head and neck cancer, but D is more active against stomach cancer, soft tissue sarcoma and melanoma. The administration of D is 100 mg/m^2 over 1 hr, for P it ranges from 135 mg–250 mg/m^2 over 3–96 hrs; the optimal regimen is not very clear. Side effects of both drugs are schedule and dose dependent with neutropenia and alopecia in common and neuropathy and some cardio toxicity for P and skintoxicity and edema for D. It is expected to take until the end of this century before we will know which of the two is optimal in which disease.

983

NEW DRUGS FOR THE TURN OF THE CENTURY

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Since the mid 1980s the focus of new drug development has shifted from analog development towards the development of new classes of drugs with new targets and new mechanisms of action. Recently it has become clear that his approach is more rewarding than analog development. Examples of new drugs emerging from the approach are the taxoid drugs and topoisomerase I inhibitors that are discussed elsewhere. Other examples are the new anti-metabolites gemcitabine and tomudex. Gemcitabine has shown interesting activity in non-small cell lung cancer, breast cancer and ovarian cancer. Issues on the optimal dose and schedule of administration have to be resolved. Gemcitabine also appears to be an attractive drug for combination with other cytotoxic agents. Tomudex is a thymidylate synthase inhibitor with interesting activity in colorectal cancer. Further randomized studies are presently being performed. Drugs interfering with the cellular signal transduction are increasingly being developed. Ether lipids have been studied in the clinic for some time, but all have witnessed their limitations. Drugs with a more specific interference with the signal transduction for instance interfere with PKC. Bryostatin recently entered clinical studies and PKC inhibitors follow. Another new class of compounds that is entering the clinic are the anti-angiogenesis inhibitors. This development is presently still limited to phase I study. New drugs that potentially may have clinical relevance for the turn of the century will be discussed.