12. Novel delivery systems and prodrugs

**062**  New drug delivery systems and their potential impact on cancer therapy

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It is increasingly recognised that success in cancer therapy not only depends on selection of the proper drug, but also on choosing the proper drug delivery system (DDS). Here the term 'drug' does not solely refer to chemotherapeutic agents but rather designates the wide variety of agents (including for example antigens and genetic material) that have been formulated in DDS for in vivo application. DDS can introduce one or more of the following favorable properties in a drug formulation:

**Direction.** DDS can target a drug to the tumor cells, thus enhancing its antitumor activity (drug targeting, site-specific delivery). DDS can also direct a drug away from those body sites that are particularly sensitive its toxic action (site-avoidance delivery).

**Duration.** DDS can act as a depot from which the entrapped drug is slowly released over time. Such a sustained release process can be exploited to maintain therapeutic (but non-toxic) drug levels in the bloodstream or at the local administration site for prolonged periods of time. Thus, DDS acted as an activity, a reduced toxicity, an increased duration of action and a decreased frequency of administration are possible beneficial consequences.

Protection. Drugs associated with DDS can be protected against the action of detrimental factors present in the host. Conversely, the patient can be protected against detrimental toxic effects of drugs (cf. Direction, Duration).

**Internalization.** DDS can promote the intracellular delivery of drug molecules that in the 'free' form would not be able to enter the cell by diffusion due to unfavorable physicochemical characteristics (e.g. DNA molecules).

**Amplification.** If the drug is an antigen, DDS can act as immunological adjuvant in vaccine formulations.

To capture recent progress, this contribution will focus on selected DDS which have made the transition from laboratory to cancer patient and in a few cases have arrived on the oncology market. The DDS selected for discussion include (1) polymeric implants, (2) DDS like polymers (e.g. SMANC5, which is commercially available in Japan) and antibodies, and (3) particulate DDS (size > 30 nm up to several μm) like liposomes (e.g. the products Doxil and DaunoXome which have reached the market) and polymeric nano/microparticles. Attention will also be paid to the rapidly developing area of cationic nonviral DDS to deliver plasmid DNA or antisense constructs.

References


**063**  Prodrugs of 5-FU

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Almost 30 years after its initial development, 5-FU remains an important element in the treatment of several common cancers. Repeated or prolonged i.v. regimes give optimal efficacy; however such schedules are relatively inconvenient. An oral formulation would therefore be an advantage, but 5-FU itself is poorly absorbed. Efforts have thus focused on developing oral 5-FU pro-drugs with better bioavailability. Much of this work has proceeded in Japan, where the drug Furtulon (5'DFUR) has been used widely. In colorectal cancer, Furtulon achieves a response rate of over 20%; however, diarrhoea was a common and troublesome side-effect, because of the liberation in the intestine of 5-FU. Capecitabine is a new drug which represents a potential advance over Furtulon. It is absorbed intact, and then converted through a 3-enzyme process (cytidine deaminase in the liver, cytidine deaminase in the liver and tumour, and thymidine phosphorylase (TP) in the tumour) to liberate 5-FU within tumour cells. As well as reducing the problem of drug-induced diarrhoea and providing prolonged tumour exposure, the requirement for activation by TP offers the extra dimension of tumour selectivity to capecitabine since this enzyme is expressed at high levels in certain tumours, including breast, colon and ovarian cancer. In phase I studies diarrhoea, nausea, neutropenia, stomatitis and hand–foot syndrome were seen using an intermittent schedule (given over 14 days, 3 weeks) and phase II studies with this schedule indicated activity in patients with paclitaxel-refractory breast cancer (25% in 100 cases, with median response duration over 8 months) and in colorectal cancer (25% in 32 patients). Phase III randomised trial results will be available shortly.

Another interesting oral 5-FU pro-drug is UFT. This contains 2 components, tegafur and uracil in a 1:4 molar ratio. Following oral administration, and rapid absorption, tegafur is metabolised in the liver to 5-FU. Uracil competes with dihydropyrimidine dehydrogenase (DPD) which is primarily responsible for the inactivating catabolism of 5-FU: thus higher plasma and tumour 5-FU concentrations are achieved, with prolonged 5-FU exposure, compared to tegafur alone. Uracil also may enhance the selective uptake of 5-FU by tumour tissue. Phase I trials (with or without oral folinic acid) indicated that diarrhoea, nausea and mucositis were dose limiting. Phase II studies in colorectal cancer indicate a combined response rate of 21% (99 pts) to UFT alone for up to 4 weeks, and 38% (140 pts) for UFT with folinic acid. Adjuvant trials of UFT in colorectal cancer show a 3 year survival benefit compared to mitomycin C.

One preclinical xenograft study showed a superior therapeutic index for capecitabine compared to UFT. This may reflect a greater degree of tumour selectivity through TP activation, but further clinical data are required to assess any differences; clearly both drugs offer a potential step forward in oral fluoropyrimidine therapy.

**064**  Antibody-directed enzyme prodrug therapy (ADEPT)


Drug resistance and lack of tumour selectivity limit the success of therapy for common epithelial cancers. In antibody-directed enzyme prodrug therapy (ADEPT) an enzyme conjugated to an antitumour antibody is given intravenously and localizes selectively in tumour. A prodrug is then given which is converted to a cytotoxic drug selectively in a tumour potentially reaching sufficient concentration locally to overcome drug resistance. Development requires analysis of the mechanism in patients. After preclinical studies and an exploratory phase I trial, a trial has been undertaken with 10 patients with colorectal carcinoma with antibody to CEA conjugated to carboplatone peptide G2 (CPEG2). A galactosylated antibody directed against the active site of CPEG2 was then used to clear and inactivate circulating enzyme. A benzoic acid mustard-glutamate prodrug was given when plasma enzyme levels had fallen to a predetermined safe level and was converted by CPEG2 in the tumour into a benzoic acid mustard. Tumour selectivity was shown with median tumour to blood ratio of enzyme exceeding 10000:1 at the time of prodrg administration. Enzyme concentrations in the tumour were sufficient to generate cytotoxic levels of active drug: The concentration of prodrug needed for optimal prodrg conversion was achieved in the plasma. Drug was detectable in plasma at approximately 1/15th of the value of prodrug showing that conversion was occurring, probably in the tumour. There was evidence of tumour response with one patient having a partial response; 6 had stable disease for a median of 4 months, one of these having a tumour marker response. Three patients had progressive tumour. Conditions for effective antitumour therapy were met and there was evidence of tumour response in colorectal cancer. ADEPT is a practical treatment which is being further developed for use in common malignancies.

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