12. Novel delivery systems and prodrugs

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 antibodies 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 tumor administration site for prolonged periods of time. This may provide, for example, 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 due for 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) soluble DDS like polymers (e.g. SMANCS, 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 Duocarmycin, which have reached the market) and polymeric nano/micro-particles. Attention will also be paid to the rapidly developing area of cationic non-viral DDS to deliver plasmid DNA or antisense constructs.

References


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 tumor 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 tumor tissue. Phase I trials (with or without oral folinic acid) indicated that diarrhea, nausea and mucositis were dose limiting. Phase II studies in colorectal cancer indicate a controlled response (7% (20 pts) to fully 5-FU alone for up to 4 weeks, and 38% (140 pts) for 5-FU with folinic acid. Adjuvant trials of 5-FU in colorectal cancer show a 3 year survival benefit compared to mitomycin C.

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 localises 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 carboxypeptidase G2 (CPG2). A galactosylated antibody directed against the active site of CPG2 was then used to clear and inactivate circulating enzyme. A benzic acid mustard-glutamate prodrug was given when plasma enzyme levels had fallen to a predetermined safe level and was converted by CPG2 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 prodrug administration. Enzyme concentrations in the tumour were sufficient to generate cytotoxic levels of active drug. The concentration of prodrug needed for optimal prodrug 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 malignanies.