A Study of Cis-Platin Effects as Anticancer Drug

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Abstract—Cis-Platin [Pt(II)(NH3)2Cl2]0 has been widely used in medicine with regard to its antitumour properties, including the treatment of various solid tumours. Despite its success, cisplatin has several disadvantages, which include severe side effects including nephrotoxicity, neurotoxicity, ototoxicity, nausea and vomiting. These toxic effects limit the dose that can be applied to patients. Herein we report the use of an injectable biodegradable polymer delivery system, to deliver cisplatin for the treatment of cancer. The association of cisplatin with long-circulating carriers alters drug pharmacokinetics and results in increased drug accumulation in tumors.

Keywords—Cisplatin, free cisplatin, Drug delivery, Anticancer drug, Control release

I. INTRODUCTION

DURING the last decades it has become clear that platinum amine coordination compounds are very interesting from a medical biological point of view. Rosenberg and his group initiated the renewed interest in these classical compounds, by studying the growth of E.coli bacteria under the influence of an electric field. This field was generated between two "inert" platinum electrodes and aqueous NH14C1 was used as an electrolyte. The bacteria showed a strong filamentous growth which initially was not understood. However, subsequent experiments by the same group soon made clear that the filamentous growth was not caused by the electric field, but by the presence of small amounts of dissolved Pt(II) and Pt(IV) compounds in the - corroding — NH14C1 solution. Detailed investigations showed that the compounds present in solution were, among others, cis- PtCl2(NH)2, trans—PtCl2(NH3)2 and some Pt(IV) compounds. In subsequent microbiological studies the cis—Pt(II) species — now called cisplatin — turned out to be the most active in causing filament formation. After these findings, tests were undertaken to study the growth—reducing capacity of cisplatin on animal tumors, such as Sarcoma 180 in Swiss white mice. The results were so positive - in many cases total regression of the tumors was observed — that clinical trials were soon thereafter scheduled and performed. The first studies demonstrated a remarkable anti—tumor activity for cisplatin. However, large-scale applications had to wait for some more years, since toxic side effects were severe. To be mentioned are [1]: nephrotoxicity, neurotoxicity, ototoxicity, nausea and vomiting [2].

So, they are administered in small doses at low concentration establishing the maximum limit dosage to 100 mg/m2 (21 days).

The clinical application of cisplatin has increased enormously mainly as a result of improved administration procedures and its use in combination therapy, i.e. the simultaneous application of a variety of synergistic anti-tumor drugs. Nowadays, usually a dosage of about 100 mg of cisplatin per m2 body surface area, dissolved in saline, is given intravenously, e.g. every month, by standard protocols. Final approval in the USA in 1979, has led to an increased number of applications of cisplatin and as a result it has become the leading and most widely used anticancer drug (30000 patients are cured each year in the USA). The drug is also registered widely in many other countries [1]. Despite causing severe side-effects, it is the preferred treatment for a variety of solid tumours, such as testicular and ovarian cancers, and is also used for treating bladder, cervical, head and neck, esophagean, and small cell lung cancer. The success in cisplatin-based chemotherapy, however, strongly depends on how careful the drug’s dosages are monitored in order to reduce severe side-effects which include nausea, vomiting, kidney damage and deafness and overcome cellular resistance [3].

Normally, platinum complexes are heavily bound to protein. Approximately 90% of bound platinum has no cytotoxicity. Only approximately 10% of free platinum was present in plasma ultrafiltrate as an intact drug [3].

II. FREE CISPLATIN

Conventional dosage forms which are still predominant for the pharmaceutical products are not able to control either the rate of drug delivery or the target area of drug administration and provide an immediate or rapid drug release. this necessitates frequent administration in order to maintain a therapeutic level. As a result, drug concentration in the blood and tissues fluctuate widely(fig. 1). The concentration of drugs may be initially high, that can cause toxic and/or side effects,
then quickly fall down below the minimum therapeutic level in time elapse. The duration of therapeutic efficacy is dependent upon the frequency of administration, the half-life of the drug, and the release rate of the dosage form. In contrast controlled release dosage forms are not only able maintain therapeutic levels of drug narrow fluctuations but they also make it possible to reduce frequency of drug administration [4].

Drugs can be dissolved or suspended in the polymer vehicle. When the polymer-drug formulation is injected into the tissue, the hydrophilic solvent dissolves, resulting in a solid implant entrapping the drug. Degradation of the polymer allows gradual release of the drug over a prolonged period. [6] the nanoparticles that be used as carrier, should have a number of important characteristics with regard to their application in drug targeting, such as biocompatibility, biodegradability, and persistence in blood after intravenous administration.

Then we report the use of an injectable biodegradable polymer delivery system, to deliver cisplatin for the treatment of cancer. This drug delivery system consists of biodegradable polymers and a biocompatible hydrophilic organic solvent that dissolves the polymer to form an injectable polymer solution. Drugs can be dissolved or suspended in the polymer vehicle. When the polymer-drug formulation is injected into the tissue, the hydrophilic solvent

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\text{% loading} = \frac{W_d}{W_{np}} \times 100 \quad (1)
\]

Where, \( W_d \) is the amount of drug (mg) found in the sample (lyophilized nanoparticles) and \( W_{np} \) is the amount (mg) of the sample (lyophilized nanoparticles) [5].

IV. BIODEGRADABLE CARRIERS

Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drug exclusively. The concept of drug targeting was first postulated by Paul Ehrlich as the 'magic bullet' (Ehrlich, 1902).

The challenges of drug targeting are: finding the proper target site for a particular disease; selecting a drug that effectively treats the particular disease; and finding an ideal carrier that carries the drug in a stable form to the specific site while avoiding the immunogenic and nonspecific interactions that efficiently clear for eignmaterial from the body (Fahmy et al., 2005)[7]. A considerable interest was established in recent years in the development of biodegradable carriers for effective delivery of therapeutic molecules at a controlled rate to the required site in the body. Such a delivery is assumed to avoid the unwanted effects of drug molecules because of controlled biodistribution. Polymeric nanoparticles are one of the promising drug delivery devices, which could meet these requirements. [8] Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained.[9] Properties of an ideal delivery system are:

a) Selectivity b) Controlled/sustained rate of release c) Immunogenicity d) Scope of disease e) Pharmaceutically acceptable characteristics (stability, administration, biodegradability, and ease of sterilization)[8] f) Surface characteristics such as charge and permeability[9] Among the various polymers, PLA, PLGA, polycaprolactone, polymethylidene malonate, chitosan and gelatin[10] are used as carrier.

V. MATHEMATICAL MODEL

In order to predict the local concentration of drug following regionalized or systemic dosing, parameters must be available that account for the transport and reaction of the drug in

Fig.1 hypothetical serum drug concentration of various oral dosage forms [4].

III. LOADED CIS-PLATIN

Cisplatin is one of the most potent anticancer agents available today. However, its use is associated with severe side effects. A more selective administration (targeting) of cisplatin to cancer cells would reduce drug toxicity and enhance its therapeutic potential. Passive targeting of anticancer drugs to tumors could be achieved by attaching them to long-circulating soluble or particulate carriers taking advantage of the “enhanced permeability and retention” (EPR) effect. The EPR effect is a result of leaky capillaries adjacent to solid tumors and a lack of a lymphatic system for the drainage of drugs back to the systemic circulation. The association of drugs with long-circulating carriers alters drug pharmacokinetics and results in increased drug accumulation in tumors, based on the EPR effect. For a more selective delivery to tumors, cisplatin has been administered in the form of soluble drug–polymer conjugates or in the form of colloidal carriers [5]. Herein we report the use of an injectable biodegradable polymer delivery system, to deliver cisplatin for the treatment of cancer. This drug delivery system consists of biodegradable polymers and a biocompatible hydrophilic organic solvent that dissolves the polymer to form an injectable polymer solution. Drugs can be dissolved or suspended in the polymer vehicle. When the polymer-drug formulation is injected into the tissue, the hydrophilic solvent

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tissue. The physical model that we have used to describe cisplatin microinfusion views that transport of the of the tissue as a convective and diffusive process. which gives way to a diffusion-reaction process as it spreads radially out ward from the matrix. The mathematical model is based on the earlier work of Batlak and Fenstermacher, Levin, Patlaks and Landahl, and Collins and Dedrick modified to account for spherical geometry and irreversible chemical reaction. Accordingly, the general transport equation is:

$$\frac{\partial C}{\partial t} = D \left( \frac{\partial}{\partial r} \left( r \frac{\partial C}{\partial r} \right) \right) + \nu_r \frac{\partial C}{\partial r} - S$$  \hspace{1cm} (2)

Where, $C$ is the concentration of cisplatin in the surrme, $D$ is the diffusion constant, $\nu_r$ is the radial velocity, $S$ is the average reaction rate of PBCA whit macromolecules in the surrme.

This equation states that the rate of change of cisplatin concentration in an infinitesimal volume is equal to the net diffusive flow into it (first right-hand term) plus the net bulk flow in to it (second right-hand term) less cisplatin bound to the macromolecules (third term).

The magnitude of the reaction term $S$ is determined by the rate of reaction of both cisplatin and the monoaquado derivative with macromolecules. When the protein nucleophile pool is not substantially depleted and the monoaquated species is at steady state, $S$ may be shown to be linearly dependent on the infusion period; $S$ = $kc$ over most of the infusion volume. Whit these approximation, eq. 2 becomes:

$$\frac{\partial C}{\partial t} = D \left( \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial C}{\partial r} \right) \right) - kc = 0$$  \hspace{1cm} (3)

The steady state solution of eq.3 can be obtained by observing that it is a modified Bessel equation and applying the appropriate boundary condition, a finite solution at infinity, and the diffusive flux relation:

$$q = -4\pi D \frac{\delta C}{\delta r}$$ \hspace{1cm} (4)

where $q$ is the mass infusion rate. The solution is [6]:

$$C(r) = \frac{q}{4\pi D} \exp(-\delta r) \frac{\exp(-\delta r)}{\delta r + 1} \frac{1}{r}$$ \hspace{1cm} (5)

Where, $\delta = \sqrt{Kc}$.

VI. CONCLUSION

Passive targeting of anticancer drugs to tumors could be achieved by attaching them to long-circulating soluble or particulate carriers.

The polymer delivery system can sustain cisplatin release. It can increase MTD and potentially enhance the antitumor efficacy of cisplatin against cancerspotentially enhance the antitumor efficacy of cisplatin against cancers.

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