

Localised Drug Delivery for the Treatment of Cancer

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Introduction

Cancer is a major global public health problem, with 1 in 4 deaths in the United States (US) and the United Kingdom (UK) due to cancer [1, 2]. However, in the US between 2006 and 2010 cancer death rates decreased by 1.8% per year in men and 1.4% per year in women, while in the last two decades cancer death rates have declined by 20% [1]. A similar trend can be seen in the UK with deaths due to cancer decreasing by 27% in males and 20% in females between 1990 and 2012 [2]. Deaths due to cancer are predicted to fall by 17% between 2011 and 2030 in the UK [3]. Treatment will depend on the type and stage of the cancer as well as the patient's general health and whether or not they will be able to tolerate the treatment. For example, early stage cancers which are localized to a particular anatomical site (i.e. cervix, bladder etc.) without evidence of spreading or intermediate cancers, with a much larger mass and/or evidence of having spread to the lymph nodes maybe removed by surgical resection followed by chemotherapy and/or radiotherapy to kill any remaining cancer cells and reduce the risk of resection, while the treatment option for late stage cancers, which have spread to other parts of the body is usually chemotherapy and/or radiotherapy. However, partial surgical

resection of late stage cancers can be used for palliative care and to improve the patient's quality of life [4, 5], but must be considered against the risks to the patient. The 5 year survival rate for most cancers is higher at either an early or intermediate stage diagnosis compared to late stage diagnosis [6]. All current cancer treatments can be very invasive and involve extended stays in or repeated visits to the hospital and in the case of chemo and radiotherapy can result in significant side-effects, reducing the patients overall quality of life during the treatment.

Localised Drug Delivery

Localised delivery of chemotherapeutic drugs offers a number of advantages over systemic administration such as direct delivery to the site of action resulting in a lower dose being required as well as a reduction in systemic side effects and increased drug stability as it remains in the delivery device until released [7]. There are two types of localised drug delivery based on their route of administration and their mechanism of action: 1) those that are delivered systemically, such as liposomes and nanoparticles and can be localised or targeted to the cancerous tissue by the addition of a targeting moiety, such as a monoclonal antibody or a chemical that is attracted to a cell marker unique to the tumour, the use of passive diffusion or by triggered release of the drug due to a change in the local environment i.e. temperature or pH. 2) Those that are implanted either directly into the tumour (particles and rods) or implanted adjacent to the cancerous tissue (rods, films, wafers or gels) after resection or ablation and act as a drug depot providing long-term and controlled drug delivery directly to the cancer

site. These devices are usually manufactured from biodegradable polymers to alleviate the need for surgical removal and the possibility of an immune response to a foreign body.

Systemically Delivered Localised Drug Delivery

Encapsulating a drug in either a nanoparticle or a liposome offers a number of advantages, such as protection from degradation in the blood stream, improved drug solubility, targeted drug delivery, decreased side-effects, increased drug exposure time and reduced drug resistance. Nanoparticles tend to be manufactured using biodegradable polymers like Poly(Lactic-co-Glycolic Acid) (PLGA) or Polycaprolactone (PCL) and have been shown to have increased efficacy and reduced toxicity compared to conventional delivery of chemotherapeutic drugs [8]. If designed correctly nanoparticle formulations can be made to accumulate in cancerous tissue by either passive or active targeting without being excreted from the body [9]. The small size of the nanoparticles allows them to accumulate in tumours by extravasation due to leaky vasculature and a poorly developed lymphatic drainage system [10, 11]. Poorly designed nanoparticles will be taken up by the Reticuloendothelial System (RES) of the body. Nanoparticles with a hydrophobic surface where rapidly taken up by the liver, spleen and lungs [12], while those with a hydrophilic surface showed an increased circulation time in the body [13]. Therefore, to achieve increased circulation time in the bloodstream and thus improved targeting, nanoparticles need to be 100

nm in size with a hydrophilic surface to reduce clearance by macrophages [14]. Paclitaxel nanoparticles have been shown to have similar efficacy, with faster administration times, when compared to conventional formulations in preclinical studies [15, 16]. Doxorubicin-loaded PLGA nanoparticles were targeted to A549 lung cancer cells by the attachment of a CXCR4 antagonist (LFC131 peptide) to their surface [17].

Liposomes are a lipid-based formulation, which have been successfully used as carriers for chemotherapeutic drugs. They have been shown to enhance the solubility of poorly water

soluble drugs, while with the addition of targeting moieties have been successfully targeted to specific cancerous tissues [18, 19]. Furthermore, liposome formulations of doxorubicin and fluorouracil have been shown to be stable for up to several years [20, 21]. A phase I clinical trial of lipoplatin, a liposome formulation of cisplatin, demonstrated improved efficacy and reduced toxicity in advanced malignant tumours [22], while a pegylated liposome formulation of gemcitabine demonstrated an increased survival rate, enhanced systemic bioavailability and a decrease or tumour growth in a mouse model, when compared to gemcitabine administered alone [23]. A number of standard non-targeted liposome formulations, such as Doxil[®], which contains doxorubicin and is used to treat breast and ovarian cancer are currently being used in the clinic [24-26], while others like lipoplatin are currently being evaluated in clinical trials [27, 28].

Actively targeted liposomes are coated with either an antibody or a ligand on their surface, to target them to specific cells, which will improve efficacy and reduce toxicity [29]. A small number of actively targeted liposome formulations have made it to the clinic, such as a transferrin-targeted oxaliplatin liposome, which reached a phase II clinical trial [30] and a doxorubicin targeted liposome which reached phase I clinical trial [31]. The high development costs such as manufacture and antibody production are limiting the advancement of actively targeted liposome formulations [32]. Another option for targeting liposomes to specific cells is triggered drug delivery, where the drug is released from the liposome in response to a change in environment, or a trigger in the targeted cell. This has the advantage of reducing side-effects by not releasing the drug in non-targeted cells. The first type of triggered liposomes were heat-triggered, whereby lipids which exhibit a phase transition just above physiological temperature, were employed to release the drug upon being taken up by the tumour cells, which were at a higher temperature due to the increased blood flow [33, 34]. The next type of triggered liposomes developed were pH-triggered liposomes, whereby a decrease in pH in the tumour cell causes the liposome to destabilise releasing the drug [35-37]. However, the slight difference in pH within the tumour

cells (6.5) compared to the blood (7.4) make it difficult to develop a liposome formulation that is stable in blood, but disrupted in the tumour cell [38].

Implantable Delivery Devices for Localised Drug Delivery

The most clinically successful and well-known implantable drug delivery device is the Gliadel[®] wafer, which is used for the treatment of recurring Glioblastoma Multiforme (GBM) and was approved by the Food and Drug Administration in 1996 [39, 40]. It is a 200mg disc-shaped, biodegradable wafer, which is manufactured using a copolymer with an 80:20 molar ratio of 1,3-bis-(p-carboxyphenoxy) propane and sebacic acid containing 3.85% w/w of the chemotherapeutic agent Carmustine. The active ingredient and polymer are dissolved in dichloromethane and subsequently spray dried into microspheres varying in size from 1 to 20µm, which are then compressed into wafers. Following the surgical resection of a primary brain tumour, up to eight wafers are implanted in the resection cavity and the Carmustine is released from the wafers over a five-day period, while the polymer matrix degrades over a period of six to eight weeks [39]. Gliadel[®] wafers provide localised delivery of a chemotherapeutic agent directly into the resection cavity and the site of the cancer. A randomised, double-blind, placebo-controlled clinical trial involving 32 patients demonstrated that the Gliadel[®] wafer increased the median survival rate, after surgery, for patients with grade IV tumours from 39.9 weeks to 58.1 weeks [40]. While a trial involving 240 participants demonstrated that the Gliadel[®] wafer (in addition to surgery and radiation) increased the median survival rate of patients with newly diagnosed high grade gliomas from 11.6 months with a placebo to 13.9 months [41]. A randomised placebo-controlled clinical trial in 222 patients with recurrent malignant gliomas demonstrated that Gliadel[®] increased the survival rate from 23 weeks to 31 weeks, while the 6 month survival rate was 50% greater in the Gliadel[®] group compared to the placebo group [42].

Another type of localised drug delivery device is polymer millirods which are small, biodegradable rods in the millimetre

range that can be implanted within a solid tumour [43], or around a solid tumour to reduce proliferation. Polymer millirods can provide site specific controlled release of chemotherapeutic drugs directly into the tumour over a sustained period of time, while reducing systemic toxicity [44]. Polymer millirods have also been investigated in reducing tumour recurrence after radiofrequency ablation, while studies have shown that drug released from a polymer millirods placed at the centre of an ablation area will have enhanced tissue penetration due to the tumour vasculature being destroyed [45]. A study in rabbits demonstrated that doxorubicin-loaded millirods placed directly into tumours of the liver, released 87% of their drug content by day 4, with a tissue penetration of 2.8mm. After 8 days the tumour size in the rabbits who received the doxorubicin-loaded millirods was significantly smaller when compared to the controls [46]. Other studies have demonstrated that the drug penetration from a millirod placed in the centre of the ablation area is significantly reduced by the formation of fibrous tissue around the ablated tissue [47]. This may limit the efficacy of this treatment as some cancerous tissue may be left outside the drug penetration region. However, it has been demonstrated that the delivery of an anti-inflammatory from a millirod reduces the formation of the fibrous tissue and thus has the potential to enhance drug penetration [48]. Therefore, the delivery of an anti-inflammatory and a chemotherapeutic drug, from a single polymer millirod, has the potential to be more effective than delivery of the chemotherapeutic drug alone.

Although wafers and polymer millirods are probably the most studied and well understood implantable drug delivery devices, there are a range of other devices such as microparticles, hydrogels and films, which are also under investigation and have shown promise in a range of *in vivo* models. Microparticles have been investigated for administration directly into the tumour via an intratumoural injection [49], or for formulation into a wafer (similar to Gliadel[®]) for implantation [50]. Thermosensitive chitosan hydrogels, which are liquid at room temperature, but gels at 37°C have been investigated for the delivery of chemotherapeutic drug directly into the tumour [51]. Due to its liquid nature the gel can be

easily injected intratumourly, where it then forms a gel slow releasing the chemotherapeutic drug. Preclinical testing using mouse models for a range of different tumour types have generated some encouraging results for the use of chitosan hydrogels in the localised treatment of cancer [52-54]. Oncogel, which has similar gelling properties chitosan as the chitosan hydrogels, but uses a Poly(Lactide-co-Glycolide) and polyethylene glycol (PLGA-PEG-PLGA) tri-block copolymer loaded with Paclitaxel [55], was tested in a phase I clinical trial involving 16 patients and was well tolerated, while paclitaxel remained localized at the injection site, minimising systemic exposure [56].

Conclusion

The use of localised delivery of chemotherapeutic drugs is mainly used as an adjuvant therapy to surgery to delay or stop the recurrence of the cancer, or as a main treatment course in cases where surgery is not available. However, localised delivery has much greater potential as a treatment than conventional systemic delivery, because recurrence occurs within the same region as the first cancer and thus localised drug delivery would allow for the sterilisation of the resection margins. This is not possible with conventional systemic chemotherapy due to a lack of local targeting. Furthermore, the use of a drug eluting implant would effectively increase the resection margins, based on how far the drug has penetrated into the surrounding tissue. This could allow for the removal of a much smaller resection area, leaving behind more normal tissue. More research needs to be done to understand the impact of the local delivery of drugs and polymer on the healing and inflammation on a tumour resection site. The development of local drug delivery devices and formulations, which reduce systemic side-effects and increase the efficacy of chemotherapeutic drugs, will be the next generation of cancer treatments.

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