Advancing the field of drug delivery: Taking aim at cancer

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Drug delivery systems for cancer therapeutics have now been used by millions of patients and have resulted in the creation of new therapies as well as significantly improving existing ones. Here we discuss a number of the drug delivery systems that have been approved by regulatory authorities and that are currently in clinical use, such as controlled delivery of cancer therapeutics, local chemotherapy, polymer drug conjugates, liposomal systems, and transdermal drug delivery patches. The next generation of "smart" drug delivery approaches such as controlled release microchips are discussed as are some of the future challenges and directions in this field.

Introduction

Few technologies have impacted cancer as broadly as drug delivery systems. Novel delivery systems have made possible the clinical use of new therapeutics, have permitted cancer treatments that have significantly reduced side effects, and have enabled new and better chemotherapeutic regimens using existing pharmaceuticals. Drug delivery systems have also facilitated cancer prevention as well as the pain management associated with cancer progression and chemotherapy. Table 1 summarizes many of the drug delivery systems currently approved by regulatory authorities and being used by oncologists. These systems are now being used by hundreds of thousands of cancer patients each year and represent a multibillion dollar a year industry. In this article, we review current methodologies for cancer drug delivery and examine future directions in this field.

## Controlled delivery of novel cancer therapeutics

Since many molecules, particularly peptides and polypeptides, have short in vivo half-lives, controlled drug delivery systems are critical to enable the protection and successful use of such drugs (Figure 1). The delivery of these molecules was once considered impossible because of the difficulty associated with the diffusion of large molecules through the materials (polymers) of conventional drug delivery (controlled release) systems (Ball, 1997). To solve this problem, it was discovered that such molecules could be physically embedded in polymers in such a manner as to create a complex network of interconnecting pores through which the drug could subsequently diffuse (Langer and Folkman, 1976). By controlling the pore structure and polymer composition, it is possible to design systems that release the drug at nearly any rate and for nearly any duration (e.g., days to years). Early studies used nondegradable polymers such as ethylene-vinyl acetate copolymer. Subsequently, lactic-glycolic acid copolymers were used to develop degradable polymer systems. This type of approach has enabled chemotherapy based on analogs of luteinizing hormone-releasing hormones such as leuprolide acetate (nanopeptides) for the treatment of advanced prostate cancer (Okada, 1997). The development of successful cancer therapy based on these molecules presented enormous challenges. The drug was initially administered orally or nasally, but only 0.05 percent and 3 percent of the drug, respectively,

were bioavailable in animals, blood levels of the drug were erratic (Okada et al., 1982), and the half-lives of these molecules when injected were only minutes. However, using the above mentioned controlled delivery approaches, drugs were physically embedded in polymers where they were released by a combination of diffusion through pores as well as polymer matrix degradation (Ogawa et al., 1988; Dijkmana et al., 1990). This approach has provided the basis for injectible delivery systems (Lupron, Zolodex, Decapeptyl) lasting from one to four months and has been successfully used by hundreds of thousands of patients (Sartor et al., 2003; Langer, 1998).

Drug lifetime can also be extended by chemical binding of drugs to water-soluble polymers such as polyethylene glycol (PEG) (Duncan, 2003). This approach can decrease immunogenicity and extend the biological lifetime of the drug. Such an approach has been used for the delivery of asparaginase, interferon, and G-colony stimulating growth factor (G-CSF).

Local chemotherapy

Cancer drugs can cause enormous toxicity; therefore, the opportunity to deliver them locally creates the possibility of improving both the safety and efficacy of cancer chemotherapy. The physical addition of a polymer to a cancer therapeutic has the advantage of enhancing the benefit of surgery while minimizing the systemic toxicity that is usually associated with standard drug treatments. The drug itself becomes more effective when placed next to, and delivered directly to, its targeted tissue and much higher local drug concentrations can be achieved compared to traditional approaches. Novel polymers such as polyanhydrides were designed and have been utilized for this purpose (Peppas and Langer, 1994). These polymers, in the form of wafers, have been used to locally deliver chemotherapeutic drugs such as carmustine (BCNU) to treat brain cancer (Brem et al., 1995). In these patients, the surgeon resects as much of the tumor as possible at the time of the operation and then places small polymer drug wafers at the surface of the brain in the tumor resection cavity (Figure 2). The drug is slowly released from these wafers for approximately three weeks to destroy any remaining tumor. Because the drug is delivered locally, rather than systemically, harmful side effects that normally occur are minimized. One clinical trial showed that after 2 years, 31% of the patients treated were alive whereas only 6%
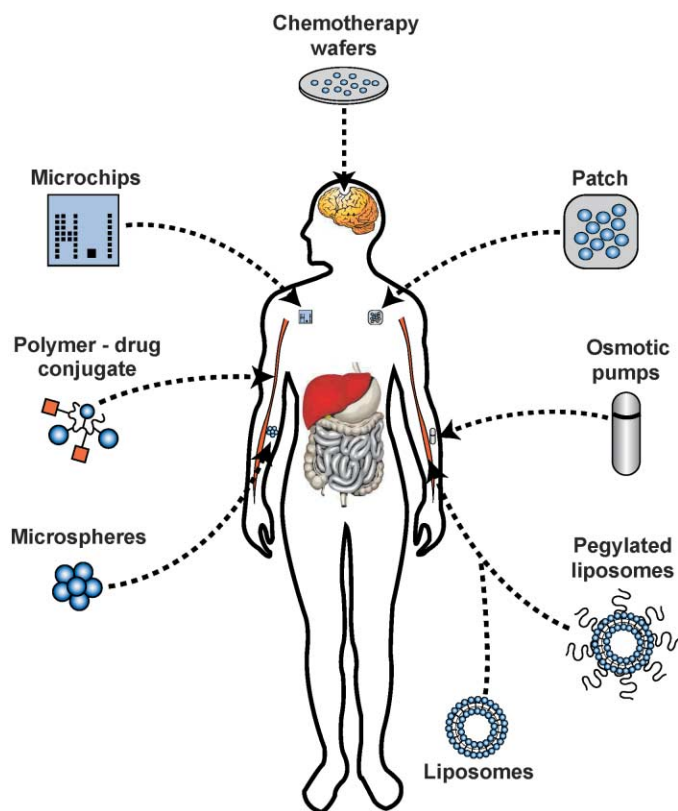
Figure 1. There are a variety of different delivery strategies that are either currently being used or are in the testing stage to treat human cancers

Examples of these include polymer microspheres impregnated with peptides that are currently being used in the treatment of advanced prostate cancer (the drug can be released through a combination of diffusion and polymer degradation), polymer wafers impregnated with BCNU that are currently being used in the localized treatment of brain cancer, osmotic pumps that are being used to deliver antiangiogenic and other drugs, liposomal systems that have been approved for use in the treatment of Kaposi's sarcoma, polymer/drug targeting moiety conjugates that are being tested against a variety of human cancers, and controlled release microchips. (Anticancer drugs are depicted in blue.)

polymers which have the effect of altering the biodistribution of the drug following intravenous administration. This approach is based on the concept that low molecular weight anticancer drugs will penetrate most tissues because they pass rapidly through cell membranes such that the drug is distributed quickly throughout the body with no selectivity toward the tumor. In the case of polymer drugs, the polymer drug linkages are designed so that they are stable in the bloodstream. This feature permits the polymer drug to circulate for a longer time than the drug itself because the higher molecular weight polymer drug system can only gain entry into the cells through endocytosis. Because most normal tissues have nonleaky microvasculatures, the polymer drug accumulates to a greater extent in tumor tissue, which has a leaky vasculature. This type of approach has been used where polymers such as N-(2-hydroxypropyl) methacrylamide (HPMA copolymer) conjugated to doxorubicin can be cleaved by specific enzymes in lysosomes. Up to 70 times more doxorubicin has been shown to accumulate in mouse melanoma tumors than in normal tissues. In addition, the maximum tolerated dose of the polymer drug is up to ten times higher than that of the free drug (Langer, 1998). Targeting moieties can also be added to the polymer to aid in treatment of specific tumors, e.g., adding galactosamine to target hepatocellular carcinoma. A variety of other polymer systems have also been developed using this approach. Currently, there are ten such different polymer drug systems at various stages of clinical trials (Duncan, 2003).

Another strategy through which drug distribution can be altered by drug delivery involves the use of liposomes. In this approach, the drug(s) are encapsulated inside liposomes that circulate throughout the bloodstream where the drug is emitted via diffusion through the liposome or by liposomal degradation. Encapsulation of the drug in a liposome reduces many of the side effects associated with certain anticancer agents such as cardiac toxicity, for instance, by preventing release of the drug at undesirably high concentrations in the body as would occur if the drug were simply injected. Attaching cancer cell-targeting ligands to liposomes in order to preferentially direct the liposomal drugs to cancer cells is an area of active research. Another important advantage of the use of a liposome as opposed to attaching a drug to a single polymer chain is that it
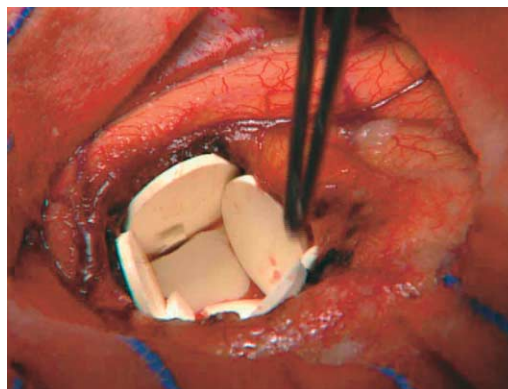
of patients receiving standard brain tumor therapies survived (Valtonen et al., 1997). This approach was approved in 1996 by the U.S. Food and Drug Administration for patients with recurrent glioblastoma, the first new brain cancer therapy approved in over 20 years. In 2003, the FDA approval was extended to include initial surgery for malignant glioma based on two additional randomized prospective studies that demonstrated improved survival and safety (Westphal et al., 2003). Studies have also reported benefit for experimental brain metastases (Ewend et al., 1998) and invasive pituitary adenomas (Laws et al., 2003). Local delivery of chemotherapeutics from long-lasting implantable lipid formulations to spinal fluid has also been used clinically to treat carcinomatous meningitis (Brem and Langer, 1996).

Targeted delivery and altering pharmacokinetics

An exciting and rapidly developing area involves developing approaches for cancer drug targeting. One method has been to couple small molecular weight chemotherapeutic drugs to

Figure 2. Polymer implants impregnated with BCNU are shown lining a human brain tumor resection cavity where the loaded drug will gradually be released as polymer wafers dissolve

Table 1. Drug delivery systems for cancer treatment and prevention currently in use

Delivery name	Drug	Type of system	Cancer treatment
Zoladex	LHRH analog	Injectable polymer rod	Advanced prostate cancer
Lypron depot	LHRH analog	Injectable polymer microsphere	Advanced prostate cancer
Decapeptyl	LHRH analog	Injectable polymer microsphere	Advanced prostate cancer
Gliadel	BCNU	Implantable wafer	Malignant gliomas
Doxil	Doxorubicin	Liposome	Ovarian cancer, AIDS-related Kaposi's sarcoma
AmBisome	Amphotericin	Liposome	Fungal Infections for patients undergoing chemotherapy
Daunoxome	Daunorubicin	Liposome	AIDS-related Kaposi's
Zinostatin (stimalmer)	SMANCS	Polymer drug	Hepatocellular carcinoma
Oncaspar	L-Asparaginase	PEGylated drug	Acute lymphoblastic leukomia
PEG intron	α-Interferon	PEGylated drug	Various cancers
Neulasta	G-CSF	PEGylated drug	Prevention of neutropenia associated with cancer chemotherapy
Duragesic	Fentanyl	Transdermal patch	Pain management
Habitrol	Nicotine	Transdermal patch	Smoking cessation—cancer prevention
Nicotrol	Nicotine	Transdermal patch	Smoking cessation—cancer prevention
Nicoderm	Nicotine	Transdermal patch	Smoking cessation—cancer prevention
Prostep	Nicotine	Transdermal patch	Smoking cessation—cancer prevention
Depocyt	Cytosine arabinocide	Lipid depot in cerebrospinal fluid	Carcinomatous meningitis

can have a much higher drug carrying capacity. However, critical issues regarding this approach that must be resolved include the prevention of the liposomes from accumulating and being cleared by the phagocytic cells of the reticuloendothelial system. One approach to reduce this involves attaching polyethylene glycol to the liposomes. Liposomal systems with duanorubicin and doxorubicin have now been approved by regulatory authorities for the treatment of HIV-associated Kaposi's sarcoma, and liposomal amphotericin B has been approved for fungal infections in cancer (Langer, 1998).

Transdermal delivery

Transdermal delivery has played an important role in both cancer therapy and prevention. Transdermal patches are composed of polymers that house the drug that will diffuse through the polymer and the skin to reach the systemic circulation. Of particular note has been the value of nicotine patches in preventing smoking and prolonging life. For example, 2 years after being on transdermal nicotine patches for 12 weeks, four times as many patch wearers did not smoke compared to patients

who received placebos (Henningfield, 1995). If one uses these studies as an estimate, over one million United States smokers have given up smoking to date due to the use of these patches. In addition, transdermal delivery systems for fentanyl are used to relieve pain in cancer patients. These systems last for 3 days and are used by hundreds of thousands of patients each year (Prausnitz et al., in press).

Targeting the tumor vasculature

A new generation of cancer therapeutics whose target is the microvasculature is in late stage clinical development. Validation of this antiangiogenic strategy to treat human cancer was recently provided by a large randomized clinical trial in which the VEGF (vascular endothelial growth factor, also known as VPF, the vascular permeability factor) antagonist bevacizumab

Figure 3. Prototype of drug-releasing microchip (Microchips, Inc.) with the capacity to deliver hundreds of doses over an implant life lasting from months to years

A: Two chips (top and bottom view) next to pencil tips. **B:** Schematic of the drug delivery microchip.
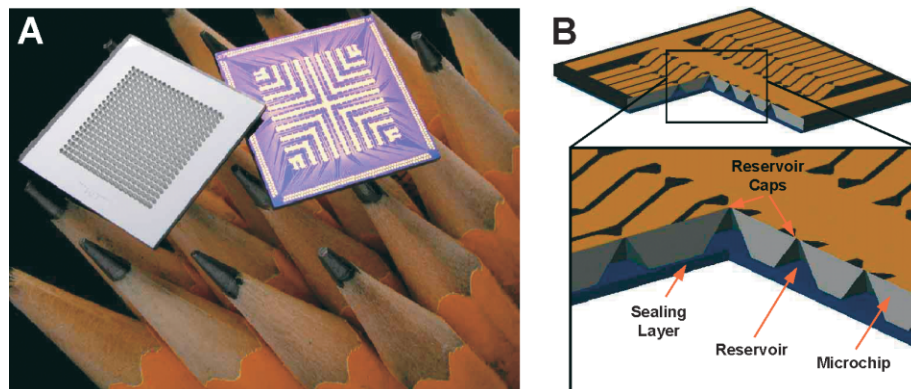
(Avastin), administered along with conventional chemotherapy, significantly improved survival of patients with colorectal cancer. Bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody, was administered in combination with the standard chemotherapy of irinotecan, fluorouracil, and calcium folinate to a cohort of over 800 patients. Patients who received the combination therapy showed a median survival time of 20.3 months compared to the 15.6 months of the placebo group (McCarthy, 2003). Controlled release polymers have proven essential in the development of bioassays for angiogenesis inhibitors since the mid-seventies (Langer et al., 1976) and have represented a method for testing the efficacy of angiogenesis inhibitors in vivo since that time (Moses and Langer, 1991; O'Reilly et al., 1994, 1997; Moses et al., 1999; Fernandez et al., 2003).

Cancer therapies that focus on suppression of the vasculature represent both interesting opportunities and important challenges for drug delivery. For example, a number of these endogenous inhibitors, for which endostatin (O'Reilly et al., 1997), angiostatin (O'Reilly et al., 1994), and troponin I (Moses et al., 1999) serve as prototypes, are proteins that require different drug delivery approaches than do smaller, synthetic drug preparations. In the case of endostatin, for example, it was demonstrated that sustained systemic delivery, as opposed to bolus administration, resulted in increased therapeutic efficacy against pancreatic cancer. This finding has led to the continuous administration of endostatin in both preclinical and clinical settings via the use of osmotic pumps (Kisker et al., 2001). In animal models, minocycline has been shown to be an effective inhibitor of angiogenesis when administered via polymer but proved to be ineffective due to toxicity when administered at high doses systematically (Weingarten et al., 1995). It may be then that local, sustained-release polymer delivery may be necessary in certain instances of antiangiogenic therapy.

Studies aimed at achieving maximum therapeutic efficacy of antiangiogenic drugs have, ironically, led to the development of "antiangiogenic scheduling" of conventional chemotherapies, an approach which has now been shown to circumvent the drug resistance induced by these same chemotherapies delivered on the traditional chemotherapeutic schedule. Delivery of the chemotherapeutic agent cyclophosphamide on a schedule that was purposefully low-dose with high frequency as opposed to classic bolus administration resulted in effective control of tumor growth with a concomitant lack of drug resistance in a number of tumor models (Browder et al., 2000; Klement et al., 2000). This low dose metronomic chemotherapy (Man et al., 2002) approach is now being tested in clinical trials at a variety of testing sites in the United States.

The unique vasculature of tumors (increased permeability, complex 3D architecture) has recently been exploited to deliver tumor-suppressing drugs with increased efficiency (Jain, 1999). Liposome-mediated delivery of anticancer drugs has improved significantly as a result of manipulating the physicochemical properties of liposomes in ways that are responsive to specific physiological features of a tumor, with the goal of optimizing the accumulation of the drug in the tumor vessels (Campbell et al., 2002).

Future considerations and challenges

Although major advances have been made in delivery of cancer chemotherapeutics, much work lies ahead. For example, localized delivery of drugs suffers from limited drug diffusion within cancerous tissues and sometimes undesirable interactions between drug and delivery vehicle. In order to address some of these challenges, increasingly smarter and more novel delivery systems are being developed. For example, a controlled release microchip that houses, and delivers on demand, many different drugs (e.g., "pharmacy on a chip") has recently been developed (Figure 3) (Santini et al., 1999; Richards-Grayson et al., 2003). These systems can potentially be preprogrammed or externally regulated to release drugs at any time, pattern, and rate. Such a system might one day enable novel combination therapies, e.g., attacking tumor cells initially with angiogenesis inhibitors followed by destroying the remaining tumor cells with chemotherapeutic drugs and then maintaining the patient on antiangiogenic therapy long term, e.g., Jain, 2001.

We are entering an era of molecular targeting of new therapies to cancer as well as of significantly improved chemotherapeutic agents. In order to most benefit from these advances, it will be necessary to be equally attentive to the development of desirable methods of drug delivery of these chemotherapeutic agents. Advances in drug delivery will allow us to improve and expand the therapeutic armamentarium against a broad spectrum of cancers.

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