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Review

Local drug delivery strategies for cancer treatment: Gels, nanoparticles, polymeric films, rods, and wafers

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ABSTRACT

Polymer-based drug delivery depots have been investigated over the last several decades as a means to improve upon the lack of tumor targeting and severe systemic morbidities associated with intravenous chemotherapy treatments. These localized therapies exist in a variety of form factors designed to facilitate the delivery of drug directly to the site of disease in a controlled manner, sparing off-target tissue toxicities. Many of these depots are biodegradable and designed to maintain therapeutic concentrations of drug at the tumor site for a prolonged period of time. Thus a single implantation procedure is required, sometimes coincident with tumor excision surgery, and thereby biodegrading following complete release of the loaded active agent. Even though localized polymer depot delivery systems have been investigated, a surprisingly small subset of these technologies has demonstrated potentially curative preclinical results for cancer applications, and fewer have progressed toward commercialization. The aims of this article are to review the most well-studied and efficacious local polymer delivery systems from the last two decades, to examine the rationale for utilizing drug-eluting polymer implants in cancer patients, and to identify the patient cohorts that could most benefit from localized therapy. Finally, a discussion of the physiological barriers to localized therapy (i.e. drug penetration, transport), technical hurdles, and future outlook of the field is presented.

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1. Introduction

Polymer-based drug delivery systems have been investigated over the last few decades as a means of achieving high therapeutic concentrations of chemotherapy to the site of malignant disease in cancer patients [1–10]. The development of these technologies is guided by the desire to improve overall survival and quality of life by increasing the bioavailability of drug to the site of disease, containing delivery to the cancerous tissues, increasing drug solubility, and minimizing systemic side effects. Existing systems can be divided into two groups based on their mode of administration and mechanism of action. The first relies on systemic delivery and consists of

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nano-materials such as polymer nanoparticles, liposomes, and dendrimers. These delivery vehicles find their target by localization to solid tumors by passive diffusion via leaky tumor vasculature, active targeting by conjugation to a chemical moiety with an affinity for an over-expressed/unique tumor cell marker (i.e. folic acid receptor, monoclonal antibody, etc.), or by triggering the release of payload from an environment-responsive nano-carrier using a local stimulus (i.e. pH, temperature, etc.). These nano-materials are predominantly intended for intravenous administration, and, while they promise the ability to target tumor tissues with accumulation of therapeutic concentrations of drug, localization is challenging due to removal and sequestration of these nanomaterials by the reticuloendothelial system. Additionally, there is a recognized need for development and validation of nano-toxicity characterization methods for obtaining reliable predictive safety information [11].

The second group of polymer delivery vehicles (and focus of this review) includes controlled release drug delivery depot systems for implantation intra-tumorally or adjacent to the cancerous tissue (Fig. 1). These technologies have been embodied in a variety of form-factors such as drug-eluting films, gels, wafers, rods, and particles and feature predictable and prolonged drug release kinetics. The majority of these devices are biodegradable so as to circumvent a second surgery for device removal and to avoid a chronic foreign-body immune response. The polymers used in these systems can be broadly divided into natural and synthetic materials. Natural polymers that have been investigated for drug delivery applications include polysaccharides such as alginate [12–14], hyaluronic acid [15], dextran [16] and chitosan [17–19] and polypeptides including collagen [20], albumin [21,22], elastin [23], and gelatin [24,25]. These materials are tolerated well *in vivo*, are available in abundance in nature, and can form hydrogels via self-assembly or by cross-linking. Furthermore, the property of spontaneous hydrogel formation of some natural polymers has been exploited to develop smart delivery vehicles that can be injected locally as a liquid, and upon exposure to changes in environment such as temperature, pH, or ionic composition, solidify into a hydrogel drug depot. Drawbacks of these materials include: 1) a necessity for high purity for biocompatibility, 2) poor solubility, particularly in organic solvents, restricting processing options and complicating the inclusion of water-insoluble chemotherapy agents, and 3) limited opportunity for chemically tuning polymer compositions to affect key properties such as drug release kinetics and degradation rate.

Conversely, the degree of customization achievable with synthetic polymers allows the application-specific design of local implants with respect to degradation, drug release, and mechanical properties. A wide range of delivery materials have been fabricated using polyesters based on lactide, glycolide, caprolactone, and dioxanone, polyanhydrides based on sebacic and adipic acid, as well as polyamides, polycarbonates, polyorthoesters, and phosphate-based polymers, which have been reviewed in detail elsewhere [7,9,10,26–28]. These polymers are often hydrophobic in nature, and are ideally suited for long-term delivery and internal stabilization of sensitive water-insoluble drugs. A significant drawback to synthetic materials is that many form acidic degradation products that can accumulate and cause inflammation at the implant site. However, this effect can be mitigated via adjustments in chemical composition and degradation profile. The aims of this article are to review the most well-studied and efficacious local polymer delivery systems from the last two decades, to examine the rationale for utilizing drug-eluting polymer implants in cancer patients, and to identify the patient cohorts that could most benefit from localized therapy.

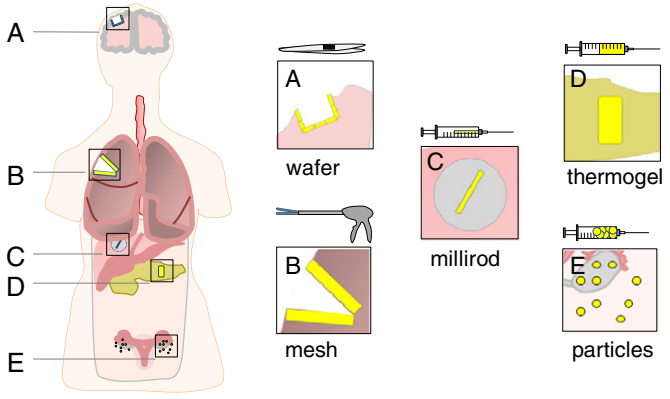

Fig. 1. Examples of localized chemotherapy delivery form factors at various treatment sites and their respective modes of administration.

2. The clinical need for localized cancer therapy

The lifetime probability of developing an invasive cancer is 44% for men and 38% for women resulting in an estimated 1,529,560 cancer diagnoses and 569,490 deaths in the US in 2010 [29]. Treatment is dictated by the cancer type, stage at diagnosis, and the patient's tolerance to the prescribed therapy. Tumors are normally classified by the TNM staging system (tumor, node, distant metastasis) which describes the extent to which the cancer has spread. Staging can be broadly divided into early, intermediate, or late stage cancers. Early stage tumors are localized to an anatomical site without evidence of spreading, intermediate cancers may include larger tumor masses and/or evidence of lymph node involvement, and late stage cancers have metastasized from their primary tissue site to other regions of the body. As evident in Table 1, for most, the majority of patients' cancers are diagnosed at local or regional stages, with 5-year survival rates varying dramatically depending on tumor type and stage. For example, locoregional prostate cancers are almost always curable, while locoregional lung cancers are significantly more difficult to treat effectively. Even those cancers that boast high 5-year survival statistics could benefit from improved control of localized disease by limiting the extent of surgical resection, circumventing radiation therapy, and avoiding various treatment toxicities, thereby maximizing preservation of functioning tissue. While the incidence of cancer mortality has steadily decreased over the last several decades due to improvements in early detection and advancements in technology, there are still major shortcomings in treatment-associated morbidity, recurrence rates, and other outcome measures with current standard of care approaches for most cancers. There are potential intervention points at each stage of cancer where localized therapy, either for curative or palliative intent, could supplement or replace existing treatments.

Surgical resection of the primary tumor and/or adjacent lymph nodes is the preferred treatment for most early stage (localized) or intermediate stage solid tumors with locoregional lymphatic involvement. The partial resection or debulking of late stage or diffuse multifocal tumors can, in some cases, have a palliative effect and improve the quality of life for some patients [30,31]. Depending on the tumor location, the benefit of removing cancerous tissue must be balanced against the resulting morbidity to the patient. Unfortunately, undetected occult microscopic disease can remain despite a complete surgical resection, and thus concurrent treatment with radiation and/or chemotherapy is often utilized with more aggressive cancer types, in an attempt to prevent recurrent tumor growth. For example, reported locoregional recurrence rates following 'curative' surgery have remained unacceptably high for some cancer types including lung (27%) [32] and colon (11%) [33]. For this reason, neoadjuvant chemotherapy and/or external beam radiation therapy are sometimes used to shrink particularly large tumors and/or 'control' regional disease prior to surgical excision, effectively 'down-staging' the disease before surgery in some patients. Radiation treatment, although generally associated with lower 5-year survival than surgery, can be curative for early stage cancers and is utilized as an alternative to resection in late stage patients including prostate, breast, and lung cancers or those