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Viewpoint

Self-healing hydrogels for enhancing chemotherapy drug efficacy: Advancements in anti-sarcoma and carcinoma therapies and clinical trial feasibility

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HIGHLIGHTS

- Site-specific administration is key for optimizing anticancer drug administration; self-healing hydrogels may allow this at reasonable costs and reproducibility.
- Self-healing hydrogels have several real-world therapeutic applications, including drug administration.
- Self-healing hydrogels are yet to be utilized for chemotherapy drug administration in clinical trials.
- Clinical research on using self-healing hydrogels in anticancer therapeutics is feasible and valid compared to other advances in anticancer drug administration.

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The incidence and prevalence of malignant tumors remain high in North America[1] despite advances in antitumor therapeutics. Modern chemotherapy drugs are associated with high costs and systemic toxicity in patients with malignant tumors such as sarcomas and carcinomas.[2,3] Administering chemotherapies with self-healing hydrogels may allow site-specific drug delivery,[4,5] which can improve the efficiency and safety of contemporary chemotherapy drugs such as doxorubicin and cisplatin for treating sarcomas and carcinomas.

Self-healing hydrogels are a class of polymers that can reform damaged bonding sites and confer greater chemical stability and durability than standard hydrogels.[4,6] Water is a major structural and functional component of hydrogels. Its aqueous constitution and healing properties confer self-healing hydrogels their injectability and enhance their ability to reach tissues specifically when injected.[7,8] Hydrogels are polymerized material, which may be formed using various techniques, such as micellar[4] and radical polymerization[6]; the latter has implications for self-healing hydrogels in drug delivery using specific reversible addition-fragmentation chain-transfer (RAFT) polymerization.[9] Injectability is the cornerstone of biomedical applications, particularly in the administration of chemotherapy drugs. However, injectability is only important *in vivo*; other *ex vivo* applications may be relevant, including tissue engineering and specific cell culture remodeling.[4,6] The most well-explored biomedical usage for self-healing hydrogels is wound healing, as these hydrogels can be modified to be both antibacterial and biomimetic (e.g., for dermal, corneal, or osseous tissues).[6,10,11] Biomimetic materials represent major advances in biotechnology. Tissue scaffold bioengineering with specific natural and more ideal synthetic properties presents greater control and efficacy over tissue replacement or tissue repair (i.e., corneal transplant, grafts, etc.).[12] Polymerized carbohydrate- and peptide-based hydrogels have been shown to significantly improve the closure time of deep wounds greater than 1 mm in diameter, without disrupting neighboring tissues with sutures or staples.[4,11,13] In addition, self-healing hydrogel dressings may be more resistant to secondary injuries by retaining their shape and constitution after damage. The biomedical applications of self-healing hydrogels are yet to be extensively tested on human tissues; however, the ability of these modifiable materials to mimic biological environments and resist damage is promising for both *ex vivo* and *in vivo* applications; self-healing hydrogels show significant potential in terms of broadly aiding therapeutics and many novel hydrogel technologies are garnering attention for human research and further academic discussion. This review of relevant studies aims to assess the differential efficacy of self-healing hydrogels within the scope of advancements in antitumor drug administration for sarcoma and carcinoma treatment, and the feasibility of developing novel clinical trials that utilize self-healing hydrogels.

Chemotherapy drugs represent a biomedical dilemma: they are one of the few prominent defenses against malignant tumors, yet their toxic

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effects are detrimental and common.[3,14] Recently, drugs such as doxorubicin and cisplatin have been widely used as first-line treatments for malignant tumors.[14] Tumors can be targeted via disrupting various biochemical processes; programmed cell death and deoxyribonucleic acid (DNA) transcription are targeted by anthracycline (e.g., doxorubicin and epirubicin)[15] and platinum-based (e.g., cisplatin and carboplatin) drugs,[14] respectively, often administered intravenously via infusion, which is not site-specific to the target tumor(s). The poor selective inhibition of these processes causes systemic toxicity. Most side effects can be similar, if not more extreme, than cancer-induced symptoms, such as vomiting, arrhythmia, kidney damage, dermal changes, and sarcopenia.[3,15,16] This does not account for the possibility of severe financial strain owing to insurance/government aid[2] or dosing complications and inconsistencies.[14]

Advances in pharmacology have produced immunostimulatory antitumor drugs that disrupt the immune system instead of systemic cell function; however, these drugs are still associated with severe patient toxicity because of inflammatory damage.[17] These drugs are immune checkpoint inhibitors; they are not site-specific because they modulate the entire system responsible for identifying immune-evasive tumor cells.[17] As mentioned previously, the primary issue with chemotherapy drugs is their site-specificity; however, this limitation pertains to the administration technique and not drug functionality. For example, doxorubicin has inherently low solubility, durability, and bioavailability, while being toxic to non-cancerous tissues upon systemic infusion.[6,15] Therefore, a carrier may be introduced to assist in its administration to the cancerous tissue. If site-specific administration of chemotherapy drugs is possible, its efficacy depends on the cancer type and the delivery mode. The transition toward nanocarrier delivery methods for antitumor drugs has been discussed for years; however, many viable research methods have not entered clinical trials.[18] Nanocarriers and nanodrugs aim to facilitate more bioavailable therapeutics while using well-established drug classes[19]; platinum nanoclusters are examples of cisplatin-like antitumor drugs that may have more ideal properties.[20] Other drugs aim to avoid the limitations of chemotherapy and immunostimulatory drugs via small molecules that target cell-signaling proteins,[21] which are often administered orally; they face resistance *in vivo*[21] and the same efficiency problems associated with inadequate site-specific transport for malignant tumor treatment.

Malignant tumors that originate in connective tissues are termed sarcomas, whereas tumors originating in the organ or skin (epithelial tissues) lining are termed carcinomas, which account for the majority of the cancer prevalence in North America.[1] Excluding skin cancers, approximately half of the female and male cancer prevalence consists of breast and prostate cancers, respectively, in the United States, as of 2022.[1,22] Hepatocellular carcinomas are associated with a lower prevalence but also much lower prognoses,[23] suggesting that the treatment of these diverse cancers must be varied and unique. Sarcoma and carcinoma treatment depends on the cancer subtype and stage; however, up-to-date biopsy techniques are equally useful for all cancers to appropriately plan treatment.[24] For some sarcomas and carcinomas, chemotherapy has reached a plateau in efficacy, in which immune checkpoint inhibitors take precedence.[23,24] Chemotherapy drugs, such as doxorubicin, have been well-studied in human models and are pertinent when administered perioperatively, especially prophylactically (i.e., postoperatively)[3]; the efficacy plateau may be overcome via implementing better administration techniques.

Self-healing hydrogels are inherently promising tools for chemotherapy drug administration owing to their modifiable durability, injectability, and ability to encapsulate hydrophilic or hydrophobic materials.[7,25] Biodegradable and biocompatible carbohydrate-based self-healing hydrogels have successfully facilitated the administration of doxorubicin via localized tumor injections; tissue pH governs both the time-controlled release[5,26] and electromagnetic radiation (EMR)-induced release (i.e., near-infrared).[27] Tumor tissue has a relatively acidic environment (pH of 6.0–6.5), aiding the site-specific release of the chemotherapy drug.[5] Avoiding systemic release can minimize cytotoxicity and enhance dosing efficacy.[5,26] The ability of hydrogels to withstand damage while transporting chemotherapy payloads is vital for improving efficiency, as injectability is the primary barrier for administration; in tandem with time-controlled or EMR-induced release, self-healing hydrogels are mechanistically relevant for anticancer treatments.[26,27] Self-healing hydrogel polymers continue to undergo novel composite modifications for drug delivery; the inclusion of ferric oxide (Fe_2O_3) in carbohydrate-based polymers may further enhance site-specific delivery guided by an external magnetic field.[28]

For sarcoma and carcinoma therapeutics, ensuring site-specific delivery is a priority. These tumors are often highly localized prior to metastasis; surgical resection is a conjunctive measure of antitumor drug administration. Thus, the therapeutic drug must allow for operative success while effectively suppressing the tumor(s). Immunostimulatory drugs effectively suppress solid tumors in most carcinomas,[17] but their inflammatory implications reduce the viability of operative procedures. These drugs, along with targeted small-molecule drugs, are not site-specific because of their biochemical functions.[21] Hence, the most reasonable modern therapeutics for sarcomas and carcinomas may be nanocarriers that transport nano-chemotherapy drugs.[15,20,29] These drugs are viable perioperatively and can be site-specific. Nanocarriers may have a unique affinity for receptors on tumor cells, even allowing enhanced drug delivery within the tumor cell[29,30] (e.g., to the nucleus); however, its accumulation within the tumor presents a challenge for these modalities.[19] Self-healing hydrogels differ from nearly all carrier mechanisms in their ability to arrive at the destination tissue despite damage (i.e., accumulation) while loading efficacious drug quantities.[26] Chemotherapy drugs loaded into injectable self-healing hydrogels are uniquely efficacious for treating sarcomas and carcinomas, with *in vivo* results confirming site specificity, low toxicity,[31] and successful postoperative prevention.[32] Furthermore, novel nano-chemotherapy drugs (*i.e.*, nano-doxorubicin and platinum nanoclusters) held within tumor-specific nanocarriers and encapsulated within self-healing hydrogels may be the optimal combined therapeutic for localized tumor administration based on current pharmacological considerations.

The lack of clinical trials and longitudinal studies using self-healing hydrogels for anti-sarcoma and anti-carcinoma therapies has limited the meaningful inferences that can be drawn regarding the long-term effectiveness and real-world feasibility of these hydrogel technologies from current research. Furthermore, as other biotechnologies and antitumor drug administration techniques advance rapidly alongside novel antitumor drugs, self-healing hydrogel-based research involving modern chemotherapy drugs may become less pertinent. However, the broad scope of therapeutic self-healing hydrogel applications increases the value of further research, regardless of advancements in competing/similar biotechnologies. Considering the feasibility of clinical trials that utilize self-healing hydrogels in administering chemotherapy drugs is important, as research that may provide knowledge from the results of these clinical trials may only continue to be relevant before other biotechnologies and antitumor drug administration techniques dominate future studies in this field.

Self-healing hydrogels have yet to receive real clinical appraisal; *in vivo* considerations are performed within animal models (i.e., rats and mice) and *ex vivo* evaluations typically use suboptimal-yield cultures, despite the continued promotion for testing novel therapeutics in the exact environment of cancer tissue development.[4,25] This limits researchers from completely evaluating and understanding the consequences of utilizing self-healing hydrogels during chemotherapy. The structural properties of current self-healing hydrogels may not be ideal for traversing the human body, based on the extended drug release parameters, individual lipid profiles (i.e., adipose and free lipids), and human enzyme interactions.[7] In general, a greater self-healing ability of a hydrogel results in weaker mechanical strength,[13] and the highly modifiable nature of self-healing hydrogels indicates the possibility of optimization; however, limitations remain with a lack of clinical trials. In

terms of feasibility for clinical trials in patients with sarcoma and carcinoma, self-healing hydrogels are readily prepared *in situ* and can remain useable for a long period[8,13]; their excellent biocompatibility in animal models provides strong evidence for feasible results in humans. Moreover, the economic demand is relatively low for a therapeutic clinical trial, considering the ability to maintain the existing chemotherapy treatment and use bulk starting material for self-healing hydrogel synthesis.[6,8,25] Clinical trials for self-healing hydrogels in antitumor treatments should be similar to the active trials for targeted small-molecule drugs, which have experienced rapid developments in clinical indications for both sarcomas and carcinomas.[21] Overall, clinical trials on using self-healing hydrogels in chemotherapeutic treatments for sarcomas and carcinomas may be feasible and clinically significant for antitumor therapeutic development.

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